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Health Assessment Document for Beryllium
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16. ABSTRACT

The properties of beryllium resemble those of aluminum, zinc, and magnesium. The main routes of beryllium intake are inhalation and ingestion. The chemical properties of beryllium are such that transformation of soluble to insoluble forms of inhaled beryllium results in long retention time in the lungs. Absorbed beryllium is deposited mainly in the skeleton, where the biological half-time is fairly long. The lung is the critical organ of both acute and chronic noncarcinogenic effects. However, the lung effects caused by chronic exposure may be combined with systemic effects. Certain beryllium compounds have been shown to be carcinogenic in various experimental animals under differing routes of exposure. Epidemiologic studies present equivocal conclusions on the carcinogenicity of beryllium and beryllium compounds. A lifetime cancer risk for continuous inhalation exposure at 1 ug beryllium/m^3 has been estimated.

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PREFACE

The Office of Health and Environmental Assessment, in consultation with other Agency and non-Agency scientists, has prepared this health assessment to serve as a "source document" for Agency-wide use. Specifically, this document was prepared at the request of the Office of Air Quality Planning and Standards.

In the development of this assessment document, the scientific literature has been inventoried, key studies have been evaluated, and summary/conclusions have been prepared such that the toxicity of beryllium is qualitatively and where possible, quantitatively, identified. Observed effect levels and dose-response relationships are discussed where appropriate in order to place significant health responses in perspective with observed environmental levels.

ABSTRACT

The chemical and geochemical properties of beryllium resemble those of aluminum, zinc, and magnesium. This resemblance is primarily due to similar ionic potentials which facilitate covalent bonding. The three most common forms of beryllium in industrial emissions are the metal, the oxide, and the hydroxide.

The main routes of beryllium intake for man and animals are inhalation and ingestion. While the absorption of ingested beryllium is probably quite insignificant, the chemical properties of beryllium are such that transformation of soluble to insoluble forms of inhaled beryllium results in long retention time in the lungs. The tissue distribution of absorbed beryllium is characterized by main depositions in the skeleton where the biological half-time is fairly long.

The lung is the critical organ of both acute and chronic non-carcinogenic effects. However, unlike most other metals, the lung effects caused by chronic exposure to beryllium may be combined with systemic effects, of which one common factor may be hypersensitization. Certain beryllium compounds have been shown to be carcinogenic in various experimental animals under differing routes of exposure. Epidemiologic studies present equivocal conclusions on the carcinogenicity of beryllium and beryllium compounds. A lifetime cancer risk for continuous inhalation exposure at 1 μg beryllium/m^3 has been estimated.

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1. INTRODUCTION

This report evaluates health effects associated with beryllium exposure, with particular emphasis placed on effects thought to be of most concern to the general U.S. population.

This report is organized into chapters which provide a cohesive discussion of all aspects of beryllium and delineate a logical linking of this information to human health risk. The chapters include: an executive summary (Chapter 2) of the information contained within the text of later chapters; background information on the chemical and environmental aspects of beryllium, including levels of beryllium in media with which U.S. population groups come into contact (Chapter 3); beryllium metabolism, where factors of absorption, biotransformation, tissue distribution, and excretion of beryllium are discussed with reference to the element's toxicity (Chapter 4); beryllium toxicology, discussing the various acute, subacute, and chronic health effects of beryllium in man and animals (Chapter 5); beryllium mutagenesis, discussing the ability of beryllium to cause gene mutations, chromosomal aberrations and sister chromatid exchanges (Chapter 6); beryllium carcinogenesis, including discussion of selected dose-effect and dose-response relationships (Chapter 7); and a human health risk assessment for beryllium, where key information from the preceding chapters is placed in an interpretive and quantitative perspective highlighting those health effects likely of most concern for U.S. populations (Chapter 8).

This report is not intended to be an exhaustive review of all the beryllium literature, but is focused upon those data thought to be most useful and relevant for human health risk assessment purposes. Particular emphasis is placed on delineation of health effects and risks associated with exposure to airborne beryllium, in view of the most immediate use intended for the present report, i.e., to serve as a basis for decision making regarding the regulation of beryllium as a hazardous air pollutant under pertinent sections of the Clean Air Act, as amended in 1977. Health effects associated with the ingestion of beryllium or with exposure via other routes are also discussed, providing a basis for possible use for multimedia risk assessment purposes, as well. The background information provided at the outset on sources, emissions, and ambient concentrations of beryllium in various media is presented in order to provide a general perspective against which to view the health effects evaluations contained in later chapters of the document. More detailed exposure assessments, taking into account even more recent, up-to-date emission and ambient concentration data will be prepared separately for use in subsequent EPA regulatory decision making regarding beryllium.

2. SUMMARY AND CONCLUSIONS

2.1 BACKGROUND INFORMATION

Even though industrial consumption of beryllium has increased 10-fold in the last 40 years, there has been no detectable change in environmental concentrations of beryllium. The primary source of atmospheric beryllium is from the combustion of coal, although the emission factors from this source are subject to controversy.

Contamination of the natural environment is largely by atmospheric deposition, as the production of solid beryllium waste appears to be negligible. Beryllium from the atmosphere eventually reaches the soil or sediments where it is probably retained in the relatively insoluble form of beryllium oxide at very low concentrations. In two hundred years since the industrial revolution, it is likely that no more than 0.1 μg Be/g has been added to the very surface of the soil, which has a natural beryllium concentration of 0.6 μg/g. Distributed evenly throughout the soil column, atmospheric beryllium could account for less than 1 percent of the total soil beryllium. Allowing for greater mobility of atmospheric beryllium in soil than natural beryllium in the inorganic soil fraction, it is possible that 10 to 50 percent of the beryllium in plants and animals may be of anthropogenic origin.

Contamination of the human environment also appears to be by the atmospheric route, as there appear to be no sources of industrial beryllium immediately influencing human consumption, except in a primary or secondary occupational setting. The normal consumption of beryllium is probably about 400 to 450 ng/day, of which 50 to 90 percent may be natural.

2.2 BERYLLIUM METABOLISM

The main routes of beryllium intake for man and animals are inhalation and ingestion. Percutaneous absorption is insignificant.

Due to the specific chemical properties of beryllium compounds, even primarily soluble beryllium compounds are partly transformed to more insoluble forms in the lungs, resulting in long retention times after exposure to all types of beryllium compounds in the lungs. Like other particulates, dose and particle size are decisive factors for the deposition and clearance of inhalec beryllium particles. Of the deposited beryllium that is absorbed, part will be rapidly excreted and part will be stored in bone.

Some beryllium is transferred to the regional lymph nodes. Beryllium transferred from the lungs to the gastrointestinal tract is mainly eliminated via feces with only a minor portion being absorbed.

There are no quantitative data on absorption of beryllium from the gastrointestinal tract in human beings, but several animal studies indicate that the absorption of ingested beryllium is less than 1 percent.

The absorption of beryllium through intact skin is very small, as beryllium is tightly bound in the epidermis.

Absorbed beryllium will go into the blood, but there are no data on the partitioning of beryllium between plasma and erythrocytes. In plasma, there are limited data suggesting that at normally occurring levels of beryllium, the main binding is to some plasma proteins. In animal experiments, it has been shown that large doses of injected beryllium are found in aggregates bound to phosphate. The smaller the dose, the more beryllium will be in the diffusible form. There are not enough data to permit an estimate of the levels of beryllium normally occurring in blood or plasma.

The tissue distribution of absorbed beryllium is characterized by main depositions in the skeleton, with other organs containing very low levels. In the liver, beryllium seems to be preferentially taken up by lysosomes. There are not enough data to permit any conclusions about the normal distribution and amounts of beryllium in the human body. The total body burden is probably less than 50 μg.

Based on animal studies, beryllium appears to have a long biological half-time, mainly depending on its storage in the skeleton. The half-time in soft tissues is relatively short.

Beryllium seems to be normally excreted in very small amounts via urine, normal levels in human urine probably being only a few nanograms per liter. Animal data indicate that some excretion via the gastrointestinal tract may occur.

2.3 BERYLLIUM TOXICOLOGY

2.3.1 Subcellular and Cellular Aspects of Beryllium Toxicity

It is not well known in what form or through which mechanism beryllium is bound to tissue constituents in normal human beings. Beryllium can bind to lymphocyte membranes, which may explain the sensitizing properties of the metal. A number of reports on experimental studies describe various *in vivo* and *in vitro* effects of various beryllium compounds on enzyme systems, especially alkaline phosphatase, to which beryllium can bind. Effects on protein and nucleic acid metabolism have been shown in many experimental studies; however, the doses in these studies have been large and parenterally administered. Because such administrative routes have little practical application to humans, the data from these studies have little utility in advancing an understanding of human effects, which are mainly on the lung. In the lung, retained beryllium particles are found in the macrophages, and the understanding of how these and other pulmonary cells metabolize beryllium is probably of most relevance for understanding chronic beryllium disease.

An important aspect of beryllium toxicology is that beryllium can cause hypersensitivity which is essentially cell-mediated. There are species differences; thus, humans and guinea pigs can be sensitized to beryllium, whereas the present data indicate that no such mechanism exists in the rat. Earlier, patch tests were used to detect hypersensitivity in humans, but these tests are no longer used since they were shown to cause a reactivation of latent beryllium disease. Presently, the lymphoblast transformation is regarded as the most useful test to detect hypersensitivity to beryllium.

2.3.2 Pulmonary and Systemic Toxicity of Beryllium in Man and Animals

There are no data indicating that moderate beryllium exposure via oral administration causes any local or systemic effects in human beings or in animals. Respiratory effects, possibly combined with systemic effects, constitute the major health effects of concern in beryllium exposures, with hypersensitization likely playing an important role in the manifestation of the systemic effects. Respiratory effects may occur as either a nonspecific acute disease or as a more specific chronic beryllium disease.

The most acutely toxic beryllium compounds are probably beryllium oxides fired at low temperatures, e.g. 500°C, and some salts, such as the fluoride and the sulfate. The latter forms of beryllium are acidic, and part of the toxic reactions caused by these compounds may be due to the acidity of the particles. Acute effects have generally occurred at concentrations above 100 $\mu g/m^3$ of beryllium, and the main feature of such effects is a chemical pneumonitis which may lead to pulmonary edema and even death. In animal experiments, concentrations of more than 1 mg/m^3 have generally been needed to produce acute effects, but effects have been reported at lower levels of exposure. In most cases, the acute disease will regress, but it may take several weeks or months before recovery is complete. If there is no further excessive exposure to beryllium, it is generally believed that acute disease will not lead to chronic beryllium disease. The amount initially deposited during acute exposure and individual predisposition are probably the main factors leading to later sequelae.

Acute beryllium poisoning was quite common in the 1940's, but since the present standards were established in 1949, the number of new cases reported has been relatively small.

Chronic beryllium disease occurred as an epidemic in the 1940's, which led to the establishment of the "Beryllium Case Registry" (BCR), a file for all cases of acute and chronic beryllium disease. Chronic beryllium disease is characterized by dyspnea, cough, and weight loss, and sometimes is associated with systemic effects in the form of granulomas in skin and muscles and effects on calcium metabolism. There are many similarities between chronic beryllium disease and sarcoidosis, but in sarcoidosis the systemic effects are much more predominant than in chronic beryllium disease. In most cases of chronic beryllium disease there are only lung effects without systemic involvement. Pathologically, the disease is a granulomatosis in which eventually there may be fibrosis, emphysema and also cor pulmonale. Resultant deaths from chronic beryllium disease are often due to cor pulmonale. A long latency time is typical to the appearance of the disease; sometimes there may be more than 20 years between last exposure and the diagnosis of the disease.

It has been very difficult to establish the levels of beryllium in air that may cause the disease. One reason for this difficulty is that exposure data have not always been obtainable. Another factor is that hypersensitization may cause the occurrence of the disease in people with relatively low exposures, whereas in nonsensitized people with much higher exposures there may be no effects. Diagnosis of the disease is obtained by X-ray examinations, but lung function tests of vital capacity may decrease before roentgenological changes are seen.

There are limited data on levels of beryllium found in the tissue of lung in cases of acute and chronic beryllium disease, and these data do not allow for conclusions about dose-effect relationships.

New cases of chronic beryllium disease are still being reported due to the fact that, in some instances, the standards have been exceeded. In industries, where the average exposure generally has been below 2 $\mu g/m^3$, there have been very few new cases of chronic beryllium disease. It is conceivable that peak exposures in such cases have exceeded 25 $\mu g/m^3$.

There have also been a large number of "neighborhood" beryllium disease cases reported. Neighborhood cases are those in which chronic beryllium disease occurs in people living in the vicinity of beryllium-emitting plants. The air concentrations of beryllium in such areas at the time when the disease has occurred has probably been around 0.1 μg/m^3, but considerable exposure via dust transferred to homes from the plants likely contributed to the occurrence of the disease. No new "neighborhood" cases of beryllium disease have occurred since standards of 0.01 μg/m^3 were set for ambient air. Present ambient air levels are generally below 1 ng/m^3.

2.3.3 Dermatological Effects of Beryllium Exposure

Contact dermatitis and some other dermatological effects of beryllium have been documented in occupationally exposed persons, but there are no data indicating that such reactions have occurred, or may occur, in the general population.

2.3.4 Teratogenic and Reproductive Effects of Beryllium Exposure

Available information on the teratogenic or reproductive effects of beryllium exposure is limited to three animal studies. The information from these studies is not sufficient to determine whether beryllium compounds have the potential to produce adverse reproductive or teratogenic effects. Further studies are needed in this area.

2.4 MUTAGENIC EFFECTS OF BERYLLIUM EXPOSURE

Beryllium has been tested for its ability to cause gene mutations in *Salmonella typhimurium*, *Escherichia coli*, yeast, and cultured human lymphocytes and Syrian hamster embryo cells; DNA damage in *Escherichia coli* and unscheduled DNA synthesis in rat hepatocytes.

Beryllium sulfate and beryllium chloride have been shown to be nonmutagenic in all bacterial and yeast gene mutation assays. This is because bacterial and yeast systems have proven to be insensitive for the detection of metal mutagens in general. Gene mutation studies in cultured mammalian cells, Chinese hamster V79 cells and Chinese hamster ovary (CHO) cells, on the other hand, have yielded positive mutagenic responses of beryllium. Similarly, chromosomal aberration and sister chromatid exchange studies in cultured human lymphocytes and Syrian hamster embryo cells have also resulted in positive mutagenic responses of beryllium. In DNA damage and repair assays, beryllium was negative in pol, rat hepatocyte, and mitotic recombination assays, but was weakly positive in the rec assay. Based on the information so far available, beryllium appears to have the potential to cause mutations.

2.5 CARCINOGENIC EFFECTS OF BERYLLIUM EXPOSURE

2.5.1 Animal Studies

Experimental beryllium carcinogenesis has been successfully induced by intravenous or intramedullary injection of rabbits, and by inhalation exposure or intratracheal injection of rats. The carcinogenic evidence for mice (intravenously injected) and monkeys and rabbits (intratracheally injected or exposed via inhalation) is presently uncertain. Guinea pigs, and possibly hamsters, have not been shown to be susceptible to beryllium carcinogenesis.

In rabbits, osteosarcomas and chondrosarcomas have been induced. These tumors have been highly invasive, metastasize readily, and are judged to be histologically similar to corresponding human tumors. In rats, pulmonary adenomas and/or adenocarcinomas of questionable malignancy have been obtained, although these studies are not well documented.

Although some studies involving beryllium clearly have limitations, the totality of the data, using the criteria of the International Agency for Research on Cancer (IARC), requires that beryllium be placed in the "sufficient evidence" category of animal carcinogens.

2.5.2 Human Studies

Epidemiologic studies present equivocal conclusions on the carcinogenicity of beryllium and beryllium compounds. Early studies (see IARC, 1972, 1980; Bayliss et al., 1971; Bayliss and Lainhart, 1972) did not provide positive evidence, but a few recent studies indicate an increased risk of lung cancer in beryllium-exposed workers. In general, the absence of beryllium exposure levels and the information on other possible confounding factors within the workplace make a positive correlation between beryllium exposure and increased risk of cancer difficult to substantiate. Epidemiologic evidence must therefore be classified as "limited" to "inadequate" according to the IARC criteria for determining carcinogenicity.

2.5.3 Qualitative Carcinogenicity Conclusions

Overall, the animal and human evidence for carcinogenicity is considered to be either in IARC Group 2A or 2B depending upon the interpretation given to the human studies. A Group 2A or 2B classification under IARC criteria means that the chemical or chemicals are probably carcinogenic for humans.

2.6 HUMAN HEALTH RISK ASSESSMENT OF BERYLLIUM

2.6.1 Exposure Aspects

In the general population, the dietary intake of beryllium is probably several micrograms but the absorbed amount will probably be extremely low due to the chemical properties of beryllium. Very little beryllium will be available in the gut for absorption. The daily inhaled amount will, for most people, probably be only a few nanograms, but it can be expected that most of the beryllium inhaled will be retained in the lungs and will eventually accumulate. The available data on levels of beryllium in the lung indicate that the lung burden in adults may be around 1 to 10 µg. The small amounts of beryllium absorbed will go to the skeleton. Since beryllium occurs in cigarettes it can be expected that smokers will absorb and retain more beryllium than nonsmokers. However, the present data on beryllium in mainstream smoke are contradictory.

2.6.2 Relevant Health Effects

Occupational exposure to various beryllium compounds has been associated with acute respiratory disease and chronic beryllium disease in the form of granulomatosis. Some systemic effects have also been noted and a hypersensitization component probably plays a major role in the manifestation of these effects. In the past, chronic beryllium disease was found in members of the general population living near beryllium-emitting plants, but past exposures were high compared to present levels of beryllium in the ambient air. No "neighborhood" cases of chronic beryllium disease have been reported in the past several years.

Numerous animal studies have been performed to determine whether or not beryllium and beryllium-containing substances are carcinogenic. Although some of these studies have limitations, the overall evidence from animal studies should be classified as "sufficient" using the evaluation criteria of the International Agency for Research on Cancer (IARC). The IARC has also concluded that the evidence from animal studies is "sufficient." Human studies on beryllium carcinogenicity have deficiencies that limit any definitive conclusion that a true association exists. Nevertheless, the possibility exists that a portion of the excess cancer risks reported in these studies may, in fact, be due to beryllium exposure. Although IARC concluded that beryllium and its compounds should be classified as having "limited" human evidence of carcinogenicity, the U.S. Environmental Protection Agency's Carcinogen Assessment Group (CAG) has concluded that the evidence can be considered as being "limited" to "inadequate."

2.6.3 Dose-Effect and Dose-Response Relationships of Beryllium

As previously stated, there are two components of chronic beryllium disease. One is a more direct toxic effect of beryllium on the lung tissue, and the other is the hypersensitization factor. Even if exposure data of high quality were available, it would still be difficult to establish dose-effect and dose-response relationships due to this hypersensitization factor. Present experience indicates that no adverse effects have been noted in industries where adherence to the 2 $\mu g/m^3$ standard has been maintained; thus, that level of beryllium in air seems to provide good protection in regard to noncarcinogenic effects. To what extent peak exposures above the present standard of 2 $\mu g/m^3$, i.e., up to 25 $\mu g/m^3$, may cause delayed effects is not clear.

From available data, the CAG has estimated carcinogenic unit risks for air exposure to beryllium. The quantitative aspect of carcinogen risk assessment is included here because it may be of use in setting regulatory priorities and in evaluating the adequacy of technology-based controls and other aspects of the regulatory decision-making process. However, the uncertainties associated with estimated cancer risks to humans at low levels of exposure should be recognized. At best, the linear extrapolation model used (see Section 7.3) provides a rough but plausible estimate of the upper limit of risk--that is, it is not likely that the true risk would be much higher than the estimated risk, but it could be considerably lower. The risk estimates presented below should not be regarded, therefore, as accurate representations of true cancer risks even when the exposures involved are accurately defined. The estimates presented may, however, be factored into regulatory decisions to the extent that the concept of upper-risk limits is found to be useful.

Both animal and human data are used to estimate the carcinogenic potency of beryllium. Most of the animal inhalation studies conducted on beryllium are not well documented, were conducted only at single dose levels, and did not utilize control groups. In the present report, data from eight rat studies were used to estimate the upper bounds for the carcinogenic potency of beryllium. The upper-bound potency estimates, calculated on the basis of animal data, range from $2.9 \times 10^{-3}/(\mu g/m^3)$ to $4.4/(\mu g/m^3)$. Among the four beryllium compounds examined in the eight studies, beryl ore is the least carcinogenically potent, while beryllium sulfate is the most potent. The estimated potency values for beryllium on the basis of animal studies, except the potency value estimated with the Wagner et al. (1980) study on beryl ore, are considerably greater than those estimated from human data. In light of the human experience in the beryllium industries, the risk estimates from animal data do not appear to be reasonable. Therefore, information from two epidemiologic studies by Mancuso (1979) and Wagoner et al. (1980) and the industrial hygiene reviews by NIOSH (1972) and Eisenbud and Lisson (1983) have been used to estimate the plausible upper bound for incremental cancer risks associated with exposure to air contaminated with beryllium. The upper-bound incremental lifetime cancer risk associated with 1 $\mu g/m^3$ of beryllium in the air is estimated to be 7.4×10^{-4}. This incremental unit risk estimate places the relative carcinogenic potency of beryllium in the lower part of the third quartile of the 53 suspect carcinogens evaluated by the CAG.

2.6.4 Populations at Risk

In terms of exposure, persons engaged in handling beryllium in occupational environments obviously comprise individuals at highest risk. With regard to the population at large, there may be a small risk for people living near beryllium-emitting industries. However, the risk for such individuals may not be due so much to ambient air levels of beryllium, but rather due to the possibility of accumulated beryllium-contaminated dust within the household. There are no data that allow an estimate of the number of people that may be at such risk, but it is reasonable to assume that it is a very small group. It should be noted that no new "neighborhood" cases of beryllium disease have been reported since the 1940's.

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3. BERYLLIUM BACKGROUND INFORMATION

3.1 GEOCHEMICAL AND INDUSTRIAL BACKGROUND

3.1.1 Geochemistry of Beryllium

Average crustal rock contains about 2.8 μg Be/g (Mason, 1966). The element occurs in more concentrated form as a component of over forty different minerals. Granites are enriched by 15 to 20 μg Be/g. It is likely that most beryllium minerals were formed during the cooling of granitic magmas (Beus, 1966), where the element was excluded during the early cooling stages and accumulated in the crystallization products of the final stages most commonly in association with quartz. The most highly enriched deposits of beryllium are found in pegmatitic intrusions.

Only two beryllium minerals are of current economic importance. Beryl, an aluminosilicate ($Be_3Al_2Si_6O_8$), is mined in the USSR, Brazil, Argentina, and the People's Republic of China, for the most part, with smaller amounts produced in several central African countries. Formed by pegmatite processes, beryl is 5- to 11-percent beryllium oxide and, in its purest gem quality form, is treasured as the green or blue emerald. Until the late 1960s, the common technique for separating beryl from associated rock was to crush the rock and hand pick the mineral crystals. By 1969, as major beryl deposits in the free world became exhausted, mechanical flotation separation techniques were developed, and a second mineral, bertrandite [$Be_4Si_2O_7(OH)_2$], became economically important (Anonymous, 1980). Bertrandite occurs as very tiny silicate granules with a beryllium oxide concentration of less than 1 percent. The only active commercial deposit of bertrandite rests at Spor Mountain, Utah. This domestic source accounts for about 85 percent of the United States consumption of beryllium ore, the rest being imported from the several countries listed in Table 3-1 (Bureau of Mines, 1982).

Beryllium was discovered by Vauquelin in 1798. The element was isolated in metallic form in 1828 by Woehler and perhaps independently in the same year by Bussy (Beus, 1966). It is a light grey, low-density metal with a high melting point, exceptional resistance to corrosion, and the capacity to absorb heat. With these properties, it is not surprising that the demand for beryllium closely parallels the growth of the nuclear, aerospace and electronics industries.

In the United States, beryllium ore is processed at Delta, Utah by Brush Wellman, Inc.

TABLE 3-1. PRODUCTION AND CONSUMPTION OF BERYLLIUM ORE (METRIC TONS)

	1948	1969	1978	1981
World production of beryl	2590	8717	2850	3857
Argentina	55	562	24	32
Brazil	1960	3900	802	590
Madagascar	10	--	12	10
Mozambique	90	132	--	20
People's Republic of China[2]	--	--	--	940
Portugal	--	31	--	20
Rwanda	11	290	63	98
South Africa, Republic of	48	340	4	108
U.S.S.R.[2]	--	1360	1900	1970
Zimbabwe	--	98	38	10
World production of bertrandite[1]	--	--	3365	5908
U.S. consumption of beryllium ore[1]	1415	--	4099	8012

[1] Calculated as the equivalent in beryl to avoid disclosing company proprietary data

[2] estimated

Source: U.S. Bureau of Mines (1982)

3.1.2 Production and Consumption of Beryllium Ore

From the ore, beryllium is extracted as the hydroxide, from which all forms of the metal and its alloys can be made. The most useful products are beryllium metal, beryllium oxide and beryllium-copper alloys. Its stiffness to-weight ratio and high thermal conductivity make beryllium metal useful in the space and aircraft industry. In the electronics industry, beryllium oxide is used to dissipate heat away from thermally sensitive components. Beryllium-copper alloys, which provide a combination of strength, electrical conductivity and resistance to stress relaxation, are used extensively for electrical/electronic switches, sockets, and connectors. The alloys are also non-magnetic. Beryllium alloys are also used in the production of dental prostheses (Newland, 1982). Other beryllium alloys are especially valuable for their resistance to oxidation or corrosion.

Although beryllium had been isolated as a metal in 1828, it was not until the 1930s that Be-Cu alloys came into widespread use. In the initial global search for beryllium, deposits of beryl known for gem production were exploited. By 1932, geochemical techniques for locating deposits by chemical anomalies in surrounding rock formations were used in the USSR (Goldschmidt and Peters, 1932). Although the discipline of geochemistry was well established, the low concentrations of beryllium in crustal rock taxed the analytical capabilities of the geochemists, and projects met with little success. Deposits of beryl remained the sole source of beryllium until 1969. Consumption of beryllium increased from 1415 tons in 1948 to 8581 tons in 1968, a 600-percent increase that was ten times the growth rate of any other common metal (Knapp, 1971). During this period, the nuclear power industry had joined the aerospace and electonics industries as a consumer of beryllium products (Anonymous, 1980). Two countries, the USSR and the United States, had become the primary consumers of beryllium ore and producers of beryllium products.

Worldwide production of beryl virtually disappeared in the Western world, decreasing from 7300 tons in 1969 to 900 tons in 1981 (Table 3-1). Production in the USSR and the People's Republic of China rose to about 2900 tons in 1981. After domestic production of bertrandite became economically feasible in 1969, bertrandite production rose to the equivalent of about 6000 tons of beryl in 1981, although this mineral contains only one tenth the beryllium of beryl. Bertrandite is mined only in the United States, although the search continues for beryl and bertrandite deposits around the world. From a domestic production of 6000 equivalent tons of beryl ore and the import of 2138 actual tons, the United States produced 130 tons of contained beryllium in 1981, of which about 40 tons were exported as finished or unfinished products.

3.2 CHEMICAL AND PHYSIOCHEMICAL PROPERTIES OF BERYLLIUM

The chemical and geochemical properties of beryllium resemble those of aluminum, zinc, and magnesium. Chemical similarities are due primarily to similar ionic potentials, which facilitate covalent bonding (Novoselova and Batsanova, 1969).

The chemistry of beryllium should be considered in the context of the three most common forms of potential industrial emissions: the metal, the oxide and the hydroxide (Table 3-2). In specific occupational settings, beryllium halides may also be important, but these are not sufficiently widespread to merit extended discussion here.

Beryllium is extracted from ores as the hydroxide and shipped in this form to commercial processing plants (Anonymous, 1980). The most common concentration process involves leaching of 20-mesh particles with sulfuric acid and hydroxylating the beryllium sulfate with di-2-ethylhexylphosphate in kerosene. The beryllium hydroxide salt is collected by filtration. The process recovers about 80 percent of the beryllium in low-grade bertrandite ore.

TABLE 3-2. PHYSICAL PROPERTIES OF BERYLLIUM AND RELATED METALS

	Be	Al	Zn	Mg
Metal				
Atomic number	4	13	30	12
Atomic weight	9.012	26.98	65.38	24.31
Atomic radius	1.40	1.82	1.53	1.72
Valence	2+	3+	2+	2+
Ionic radius Å	.35	.51	.74	.66
Density 25°C	1.85	2.7	7.14	1.74
Melting point	1283°C	660.4	419.58	648.8
Boiling point	2970°C	2467	907	1107
Thermal conductivity 100°	.401	.573	1.12	.376
Electrical resistivity μ°nm · cm @ 20°C	4.31	2.65	5.916	4.45
Oxide				
Formula	BeO	Al_2O_3	ZnO	MgO
Molecular weight	25.01	101.96	81.37	40.31
Density	3.008	3.965	5.606	3.58
Melting point	2530	2072	1975	2852
Boiling point	3900	2980	---	3600
Thermal conductivity 725°C cal/sec · cm² · °C/cm	.111			
Hydroxide				
Formula	$Be(OH)_2$	$Al(OH)_3$	$Zn(OH)_2$	$Mg(OH)_2$
Molecular weight	43.01	78.00	99.38	58.33
Density		2.42	3.053	2.36
Solubility M/ℓ	0.8×10^{-4}			
Decomposes to oxide at °C	250-300	300	125	350

From beryl, beryllium may be extracted by the Sawyer-Kjellgren process, where the ore is melted at 1625°C and cooled quickly with water to form a beryllium glass. The glass is dried and ground to 200-mesh powder, then leached with sulfuric acid. Sodium hydroxide is used to convert the sulfate to beryllium hydroxide. This process is also about 80-percent efficient but is not effective with the low beryllium concentration in bertrandite ore.

A third process, the Copaux-Kawecki process, uses sodium ferric fluoride to extract beryllium from low-grade, fine-grained ores at a 90-percent efficiency. This process is no longer used in the United States and Europe, due to the higher expense and to the toxicity of beryllium fluoride. Indeed, the first medical report of berylliosis in 1933 can be attributed to exposure to beryllium fluoride at an extraction plant (Weber and Englehardt, 1933).

Waste materials from the production of the raw beryllium product can result in elevated environmental concentrations of beryllium hydroxide and lesser amounts of beryllium fluoride. These would be confined to the waste facilities used by the only ore-processing plant in the United States, operated by Brush Wellman at Delta, Utah. Conversion of the hydroxide to the oxide or pure metal form takes place at Brush Wellman facilities in Delta, Utah and Elmore, Ohio.

About 10 percent of the domestic beryllium hydroxide is used for the production of pure beryllium metal in sheet, rod, or wire form. Since 1979, Brush Wellman, Inc. has been the only free-world producer of beryllium metal (Anonymous, 1980). The metal is milled to desired specifications at the user facility, producing beryllium dust and scrap in the vicinity of machine shops. Because of the high cost of the metal at this point, efficient recovery and recycling of the metal receive a high priority.

Beryllium oxide (beryllia) production consumes about 15 percent of the raw beryllium hydroxide in the production of high-technology ceramics that have superior thermal conductivity, especially at high temperatures. These products make good electrical insulators and have a high resistance to thermal shock. The high melting point permits the use of beryllium oxide in rocket nozzles and thermocouple tubing (Table 3-3).

The remaining 75 percent of beryllium hydroxide is used in the production of alloys, primarily Be-Cu alloys. As a general rule, 2 percent beryllium in a copper alloy with an array of other metals can markedly increase the strength, endurance, and hardness of the alloy. Most applications are in the electronic field, although specialized uses such as springs, wheels, and pinions serve an indispensable industrial function. Kawecki-Berylco, Inc. at Reading, Pennsylvania, and Brush Wellman at Elmore, Ohio are the major producers of beryllium alloys in the United States.

3.3 SAMPLING AND ANALYSIS TECHNIQUES FOR BERYLLIUM

Trace amounts of beryllium occur in environmental samples at concentrations of about 0.01 to 0.1 ng/m^3 in air, 0.05 to 0.1 μg/g in dust, 0.01 to 1.0 ng/g in surface waters, 0.3 to 6 μg/g in soil, and 0.01 μg/g in biological materials. Some plants, such as hickory, may accumulate beryllium as much as

TABLE 3-3. INDUSTRIAL USES OF BERYLLIUM PRODUCTS

Beryllium Metal

aircraft disc brakes
navigational systems
X-ray transmission windows
space vehicle optics and instruments
aircraft/satellite structures
missile parts
nuclear reactor neutron reflector
fuel containers
precision instruments
rocket propellants
heat shields
mirrors
nuclear weapons

Beryllium Oxide

high-technology ceramics
electronic heat sinks
electrical insulators
microwave oven components
gyroscopes
military vehicle armor
rocket nozzles
crucibles
thermocouple tubing
laser structural components

Beryllium Alloys

springs
electrical connectors and relays
pivots, wheels and pinions
plastic injection molds
precision instruments
aircraft engine parts
submarine cable housing
non-sparking tools

1 μg/g dry weight (Newland, 1982). Consequently, the collection and pretreatment of samples is determined by the capabilities of the method of analysis. Two techniques, gas chromatography (GC) (Ross and Sievers, 1972) and atomic absorption spectroscopy (AAS) (Owens and Gladney, 1975) appear to give the best combination of sensitivity and sample handling efficiency. Colorimetry, fluorometry, and emission spectrometry are occasionally used.

Because of interfering substances and low environmental concentrations, samples analyzed by atomic absorption spectroscopy and gas chromatography require pretreatment. At high concentrations (500 μg/g), aluminum and silicon interfere with beryllium analysis by AAS. Separation is by chelation and extraction with an organic solvent. The limit of detection for the flame method of AAS is 2 to 10 ng/ml, and 0.1 ng/ml for the flameless method. Air samples of a few cubic meters must be concentrated after extraction to a volume of less than 1 ml to enter the detection range. The high-volume sampler normally used in sampling networks collects in the range of 1.1 to 1.7 m^3/min and is therefore more desirable in terms of sample size than a low-volume sampler which collects at 0.001 m^3/min, or a cascade impactor at the same flowrate. Normal concentrations of dust, water and biological materials are all at or below the detection limits of flameless AAS, so that preconcentration by wet digestion is required.

Ross and Sievers (1972) report a detection limit of less than 0.04 ng/m^3 in air analyzed by GC, making this method marginally acceptable for small sample sizes. Extensive chemical digestion and extraction is required, however.

For any method, standard reference materials are available in the form of fly ash, coal, orchard leaves, and bovine liver. Owens and Gladney (1975) have reported the beryllium values for these SRM's.

3.4 ATMOSPHERIC EMISSIONS, TRANSFORMATION AND DEPOSITION

There is little evidence for significant emissions of beryllium to the atmosphere during ore production. Uncontrolled emissions during ore processing could be locally significant without existing regulations. The 20 percent of the beryllium lost as waste represents a potential environmental problem.

Emission of beryllium from non-metallurgical sources amounts to 99 percent of U.S. emissions (Table 3-4). The average concentration of beryllium in coal is between 1.8 and 2.2 μg/g. In 1981, the United States burned 640 x 10^6 metric tons of coal. Had emission control measures for other pollutants not been used, 1,300 tons of beryllium would have been emitted, or about 10 times the annual U.S. production of contained beryllium metal. But emission control measures are used and there is evidence that 70 to 90 percent of this beryllium is retained by the captured fly ash. The actual efficiency of beryllium retention is a subject of controversy and a source of confusion in several published reports. Phillips (1973) presented data which suggested 86 percent

TABLE 3-4. NATURAL AND ANTHROPOGENIC EMISSIONS OF BERYLLIUM*

Natural	Total U.S. Production (10^6 t/yr)	Emission Factor (g/t)	Emission (t/yr)
windblown dust	8.2	0.6	5
volcanic particles	0.41	0.6	0.2
Total			5.2
Anthropogenic			
coal combustion	640	0.28	180
fuel oil	148	0.048	7.1
beryllium ore processing	0.008[†]	37.5[†]	0.3
Total			187.4

*Units are in metric tons

[†] Since the production of beryllium ore is expressed in equivalent tons of beryl, the emission factor of 37.5 is hypothetical.

of the beryllium in coal is released to the atmosphere. Gladney and Owens (1976) concluded that only 4 percent escapes. Henry (1979), in a report to the U.S. Environmental Protection Agency, suggested that less than 1 percent escapes, but that 35 percent remains unaccounted for in mass balance estimates. A closer look at these three calculations may reveal a part of this discrepancy.

All three authors use a mass balance calculation, where the concentration of beryllium in the coal and the fly ash is known. Since beryllium output is assumed to be confined to captured fly ash and emitted stack gases, that fraction of the coal input not found in the fly ash is considered as emitted to the atmosphere. Neither Phillips (1973) nor Gladney and Owens (1976) knew the actual mass of the ash produced. In both cases, they reported ash content published elsewhere in the literature. Phillips measured a beryllium content of the coal and ash of 2.5 and 5.0 μg/g, respectively, and assumed an ash content of 7 percent to calculate the fraction not collected as

$$\frac{2.5\ \mu g/g - (0.07)\ (5\ \mu g/g)}{2.5\ \mu g/g} = 0.86$$

Gladney and Owens (1976) assumed an ash content of 12 percent and measured a coal and ash beryllium content of 1.89 and 15.3, respectively. The calculated percent loss would be

$$\frac{1.89\ \mu g/g - (0.12)(15.3\ \mu g/g)}{1.89\ \mu g/g} = 0.0285$$

Analytical errors aside, both calculations are extremely sensitive to the assumed ash content of coal, which varies between 7 and 14 percent. Using this range, the data of Phillips show beryllium losses of 72 to 86 percent and the data of Gladney and Owens, 0 to 43 percent. It is also possible that errors of analysis were made. Coal and ash from the same plant that Phillips investigated were reported by the Southwest Energy Study (1972) to be 0.43 and 7 μg Be/g, respectively. In the range of 7 to 14 percent ash, these data would yield a percent beryllium loss of less than zero, however. If the average beryllium content of western coal (1 μg/g) is used with the Phillips data, the loss to the atmosphere ranges from 30 to 65 percent.

Henry (1979) made similar measurements of coal and ash. Sixty-five percent of the beryllium was accounted for in the ash. However, measurements of beryllium at the precipitation outlet and in the stack did not account for the remainder of the beryllium. In simulation runs, Yeh et al. (1976) found 77 percent retention of the beryllium in the slag and fly ash.

It seems reasonable to conclude that between 10 and 30 percent of the beryllium in coal is emitted to the atmosphere from coal during the combustion process. While not all coal burning facilities control emissions to the extent of power plants, the following calculation is a conservative estimate of total beryllium emissions from coal in the United States during 1981.

$$640 \times 10^6\ \text{t coal/yr} \times 1.4\ \text{g Be/t coal} \times \underset{\text{efficiency}}{(0.1\ \text{to}\ 0.3)} = 180 \pm 90\ \text{t Be/yr}$$

Emission from oil-burning facilities may be calculated from the average beryllium concentrations of fuel oil (Anderson, 1973), an assumed loss of 40 percent, and a consumption of 1.1×10^8 tons residual oil per year. From this calculation, it appears that 7.2 tons beryllium are emitted from this source.

Although no data exist, it is likely that no more than 0.5 percent of the contained beryllium is emitted during the metallurgical process, or about 0.12

tons/year. Therefore, 185 tons/year would seem to be a reasonable estimate for anthropogenic beryllium emissions from the United States. Assuming a residence time of 10 days, an effective stratospheric volume of 2.3×10^{16} m^3, and stationary air mass above the United States, this amount of beryllium could account for an average atmospheric concentration of 0.22 ng/m^3. Because of the dispersion caused by moving global air masses, the actual air concentration averages about 1/3 this value. The report by Flinn and Reimers (1974) that coal combustion accounts for 88 percent of the total beryllium emissions was conservative and could perhaps be revised upward to 95 percent.

Because most atmospheric beryllium derives from coal combustion, it is likely that the chemical form is beryllium oxide. Conversion to the ionized salts is possible, but not reported in the literature. Gladney and Owens (1976) discuss particle size distributions of stack emissions, reporting that most of the beryllium may be found on particles smaller than 1 µm. These particles remain aloft for about 10 days.

Removal from the atmosphere is by wet and dry deposition. Dry deposition of aerosol particles is a function of particle size, windspeed and surface roughness, not of the chemical properties of the element. The deposition rate of beryllium has not been measured, but can be calculated by analogy to other elements. Davidson et al. (1982) have described the relationship between air concentration, particle size and surface roughness. For vegetation surfaces and particles in this size range, a reasonable deposition velocity would be 0.25 cm/sec. At an average air concentration of 0.1 ng/m^3, beryllium would be removed from the atmosphere at a flux of 0.002 ng/day for each square centimeter of actual surface area. The ratio of actual to plane projected surface area normally ranges from 1 to 20, so that deposition flux may vary by this factor based on surface characteristics alone.

On a more general level, Kwapulinski and Pastuszka (1983) have determined that, in Poland, emissions of beryllium are in balance with deposition and that the solution of the Reynolds mass balance model described by Astarita et al. (1979) applies to beryllium. This model describes deposition as a function of air concentration. The coefficient of deposition, K_1, was found to be constant during rainy periods and linearly correlated with windspeed during non-rainy periods. This report confirms that beryllium is removed from the atmosphere by both wet and dry deposition in a manner similar to metals on particles of comparable size distribution. Because K_1 varies regionally with surface roughness and windspeed, and because the values for K_1 have not yet been measured in the United States, the preceding calculations based on metals of similar particle size are an acceptable substitution.

There are no reports of beryllium concentrations in precipitation. If half the emissions return to the surface of the earth as wet precipitation, the average concentration of beryllium in rain or snow would be 0.01 ng/g, which is far below the detection limit of most analytical techniques. Meehan and Smyth (1967) reported an average of 0.07 ng/g in rain in Australia.

Beryllium oxide is very insoluble and would not be mobilized in soil or surface water, at environmental pH ranges of 4 to 8. If this is indeed the chemical form of beryllium at the time of deposition, beryllium would not move easily along grazing food chains, but would be confined to soils and sediments. If, however, significant amounts of beryllium are converted to chloride, sulfate, or nitrate during atmospheric transport, solubility upon deposition would be greatly enhanced and mobility within ecosystems could be facilitated. Biochemically, beryllium is classified as a fast-exchange metal, a property that potentially allows beryllium to interfere with the transport of nutritive metals such as calcium into eucaryotic cells (Wood and Wang, 1983). There is a need for further research on the effects of pH on the mobility of beryllium in ecosystems and the subsequent effects on plants and animals. While further discussions of the effects of beryllium on natural populations of plants and animals are beyond the scope of this document, it is worth noting that some toxic effects have been reported. These are reviewed by Brown (1979).

3.5 ENVIRONMENTAL CONCENTRATIONS OF BERYLLIUM

3.5.1 Ambient Air

Beryllium is measured at many of the stations in the SLAMS (State and Local Air Monitoring Stations) and NAMS (National Air Monitoring Stations) networks. The data are available from the SAROAD data base of the U.S. Environmental Protection Agency. The detection limit for these analyses is 0.03 ng/m^3 and most annual averages are at this concentration. Annual averages which exceeded 0.1 ng/m^3 during 1977-81 are listed in Table 3-5. The highest 24-hour observation was 1.78 ng/m^3 reported in Atlanta, Georgia during 1977. There were no locations where the 30-day average concentration approached the 10 ng/m^3 standard set by the U.S. Environmental Protection Agency, (FR, 1973).

TABLE 3-5. CONCENTRATIONS OF BERYLLIUM IN URBAN ATMOSPHERES

Values exceeding 0.1 ng/m^3 are reported for the period 1977-81. Some values for 1981 are not yet available. Units are in ng/m^3. Values in parentheses are the number of 24-hour observations used to determine this average annual air concentration.

	1977	1978	1979	1980	1981
Birmingham, AL		.11(20)			
Douglas, AZ				.25(7)	
Tucson, AZ					.11(7)
Ontario, CA				.14(11)	
Hialeah, FL					.22(1)
Miami, FL	.11(20)				
St. Petersburg, FL	.12(13)				.11(7)
Tampa, FL	.11(23)	.11(22)			
Atlanta, GA	.19(27)	.13(24)			
East Chicago, IN		.11(18)			
Gary, IN		.15(25)	.16(21)		
Hammond, IN			.12(23)		
Indianapolis, IN			.11(19)		
Des Moines, IA					.11(6)
Kansas City, KS		.14(28)			
Ashland, KY	.16(23)	.37(19)			
Baton Rouge, LA	.19(26)				
Portland, ME				.18(5)	
Baltimore, MD				.11(6)	
Fall River, MA		.11(29)			
New Bedford, MA		.12(26)			
Flint, MI				.13(10)	
Lansing, MI					.13(4)
Kansas City, MO		.12(29)			
Omaha, NB		.13(15)			
Camden Co., NJ	.22(24)			.17(14)	
Perth Amboy, NJ		.13(28)			
Trenton, NJ			.11(19)		
Albuquerque, NM					.22(6)
Niagara Falls, NY		.17(5)			
Syracuse, NY		.19(2)			
Cincinnati, OH		.11(30)		.11(16)	
Cleveland, OH		.15(26)			
Columbus, OH		.11(26)			
Dayton, OH		.21(26)			
Mansfield, OH		.15(29)			
Portsmouth, OH		.14(27)			
Steubenville, OH		.13(24)	.17(28)		
Toledo, OH				.11(11)	
Youngstown, OH		.19(27)	.14(26)	.18(10)	

(continued on the following page)

TABLE 3-5. (continued)

	1977	1978	1979	1980	1981
Guayanilla Co., PR					.15(7)
Baja Co., PR				.17(5)	.16(5)
Knoxville, TN		.11(29)			
Nashville, TN			.13(11)		
Dallas, TX		.14(25)	.40(2)		
El Paso, TX		.17(17)			
Houston, TX	.11(15)				
Lubbock, TX				.17(13)	
Pasadena, TX		.13(23)			
Seattle, WA					.11(7)
Charleston, WV		.15(23)			
Milwaukee, WI		.13(25)			

3.5.2 Soils and Natural Waters

Shacklette et al. (1971) reported a geometric mean of 0.6 µg Be/g in soil for 847 samples distributed evenly across the United States. Only 12 percent of the samples exceeded 1.5 µg/g. The soils were sampled at a depth of 20 cm to avoid surface contamination. These results are lower than those of previous geochemical surveys by Vinogradov (1959), Hawkes and Webb (1962), and Mitchell (1964), all of whom reported means of 6 µg/g. The differences can most reasonably be explained by limitations in analytical techniques. Nevertheless, the 0.6 µg/g average is somewhat consistent with the average crustal value of 2.8 reported by Mason (1966).

Global values for beryllium in natural surface waters range from 0.01 to 1.0 ng/g (Bowen, 1979). The lowest value (0.01 ng/g) was reported by Meehan and Smythe (1967) in Australia. These concentrations are in the same range as the calculated concentration of beryllium in precipitation (0.01 ng/g) discussed above. Seawater was reported to be 0.0005 ng/g by Merrill et al. (1960) and 0.0056 ng/g by Bowen (1979). There are no available reports of beryllium in groundwater.

3.6 PATHWAYS TO HUMAN CONSUMPTION

The possible sources of human consumption of beryllium are inhaled air, food, drinking water, and ingested dusts. The environmental sources of beryllium which can lead to human consumption are shown in Figure 3-1. In this

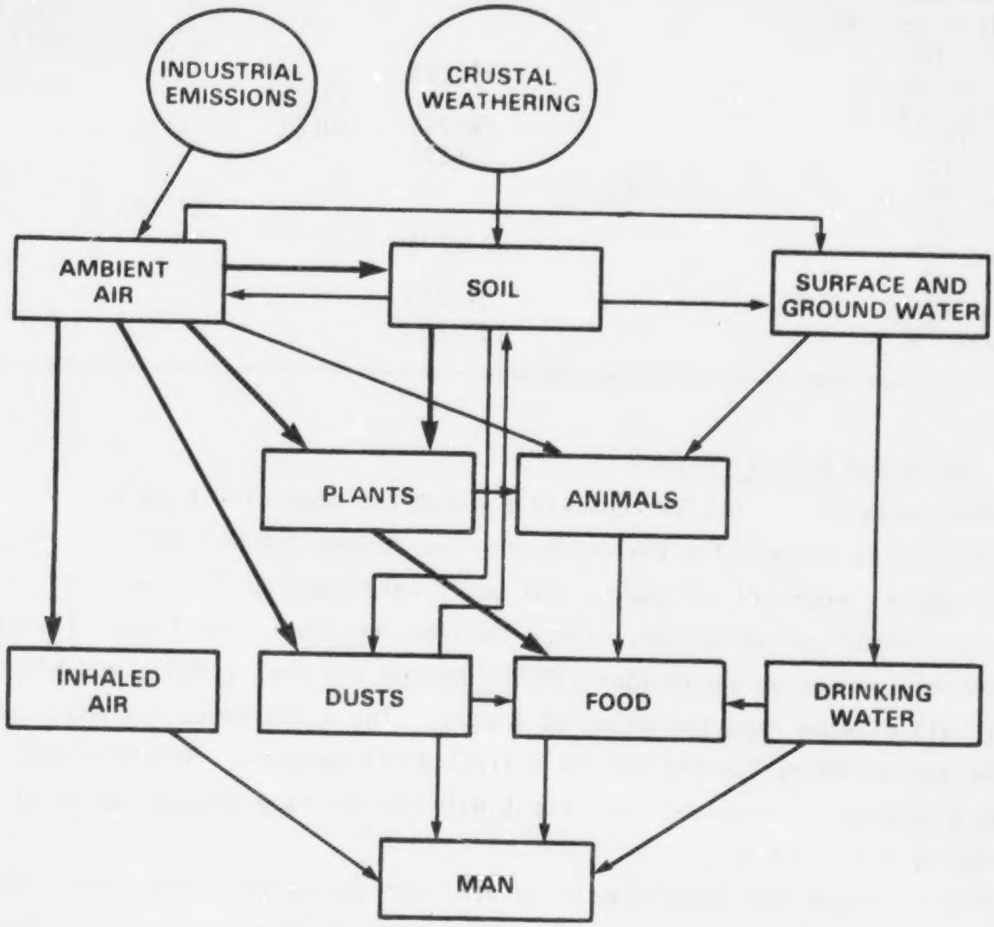
INDUSTRIAL EMISSIONS
CRUSTAL WEATHERING
AMBIENT AIR
SOIL
SURFACE AND GROUND WATER
PLANTS
ANIMALS
INHALED AIR
DUSTS
FOOD
DRINKING WATER
MAN

Figure 3-1. Pathways of environmental beryllium concentrations leading to potential human exposure.

section, beryllium concentrations in the four compartments immediately preceding human consumption are estimated for a typical background human environment not exposed to extraordinary sources of beryllium. These values are combined with known consumption rates for air, food, water and dust to estimate the typical daily consumption of beryllium. The value of this determination lies not in its precision, but in its ability to eliminate misguided estimates of human consumption which are exceptionally high or low.

Because of the sporadic location of stations reporting atmospheric concentrations of beryllium, the average of reports may be biased toward the high region. A probable average concentration for air concentration would be 0.08 ng/m^3 for residential environments not located near an unusually high source of beryllium. The 0.08 ng/m^3 value as measured at a monitoring station could be influenced by vertical and horizontal distance from the source and by an indoor vs. outdoor environment of filtered or unfiltered air.

Limited data for foods are available. Meehan and Smythe (1967) analyzed a few foods from Australia, reporting values from 0.05 to 0.15 ng/g fresh weight. Beryllium in drinking water appears to range from 0.01 to 1.2 ng/g, with an average of 0.2 ng/g. There are no reports of beryllium in household dust, but if it is assumed that this dust is derived solely from the atmosphere, an air/dust ratio of 600 would be a reasonable estimate. At 0.1 ng/m^3, household dust would contain 60 ng/g.

The average American adult inhales 20 m^3 of air/day, and consumes 1200 g of food and 1500 g of water and beverages (Pennington, 1983). The daily consumption of dust is not well established, but a conservative estimate of 0.02 g is made here for the purpose of illustration. The data in Table 3-6 show that the typical American adult consumes 423 ng/day of beryllium, most of which comes from food and beverages. This calculation shows that direct air inhalation or the consumption of dust derived from air have little impact on the total consumption of beryllium. This overall determination is extremely sensitive to the average concentration of beryllium in food and water (99.3 percent of total daily consumption). It is likely that there is some variation in these numbers according to the types of food and beverages eaten, and that there is some atmospheric contribution to the beryllium concentrations of food and beverages.

Daily consumption from extraordinary sources, such as occupational exposures or secondary occupational exposure to workers' families, would cause increases in the air and dust categories. At 2 μg/m^3 air concentrations (the

TABLE 3-6. POTENTIAL HUMAN CONSUMPTION OF BERYLLIUM FROM NORMAL SOURCES IN A TYPICAL RESIDENTIAL ENVIRONMENT

	Environmental Concentration	Total Daily Human Intake	Consumption	Percent of Total Daily Consumption
Air	0.08 ng/m^3	20m^3	1.6 ng/day	0.4%
Food	0.1 ng/g	1200g	120	28.4%
Water	0.2 ng/g	1500g	300	70.9%
Dust	60 ng/g	0.02g	1.2	0.3%
		Total	422.8	

current occupational standard), a worker's exposure for an 8-hour shift would increase to more than 13,000 ng/day. Dust of beryllium metal or metal oxide, at a daily consumption of 0.02 g (including dust consumed during the working shift and that carried home on the clothing of the worker), could add 2,000,000 ng beryllium to the total daily consumption. There is also the possibility that certain individuals might be exposed to beryllium from implanted dental prostheses. Although the leaching of nickel and chromium from alloys used in prostheses has been reported, no studies of beryllium are available.

4. BERYLLIUM METABOLISM IN MAN AND ANIMALS

4.1 ROUTES OF BERYLLIUM ABSORPTION

4.1.1 Beryllium Absorption by Inhalation

There are no data on deposition or absorption of inhaled beryllium in human beings. However, it can be expected that beryllium particles will follow the same general laws as other inhaled particles in that dose, size and solubility will be important factors for deposition and clearance.

Beryllium has been found in lungs of persons without known occupational exposure to the metal. Cholak (1959) analyzed 70 lungs from unexposed individuals and reported an average concentration of 3.3 μg Be/kg dry weight (range: 0.1-19.8 μg/kg). Meehan and Smythe (1967) reported a mean level of 1.3 μg/kg wet weight (range: 0.3-2.0 μg/kg) in 4 human lungs corresponding to about 6 μg/kg dry weight. Sumino et al. (1975) analyzed beryllium in the lungs of a few Japanese subjects and found concentrations of up to 30 μg/kg wet weight. In viewing these above findings, it should be kept in mind that smoking habits were not taken into account. In addition, it is difficult to validate such data, as well as other data on beryllium in tissues or body fluids, since there have not been any interlaboratory or quality control studies. There are no reference samples for beryllium in tissues or body fluids. The data by Cholak have been used as a basis for determining an upper normal level of beryllium in lung of 20 μg/kg dry weight.

Animal studies have shown that rats exposed to beryllium sulfate (average beryllium concentration of 35 $\mu g/m^3$) for 7 hr/day, 5 day/week, for 72 weeks, reached a plateau in lung beryllium concentrations after 36 weeks of exposure. A plateau in the tracheobronchial lymph nodes was also reached at that time. After cessation of exposure, pulmonary beryllium was first eliminated with an initial half-time of two weeks, followed by much slower elimination (Reeves et al., 1967; Reeves and Vorwald, 1967).

In studies which have examined the distribution of radioactive beryllium compounds via intratracheal injection, Kuznetsov et al. (1974) reported a half-time of 20 days in rats given a single injection of beryllium chloride, whereas Van Cleave and Kaylor (1955) reported that the citrate was rapidly eliminated in rats. Longer observation periods in rats, however, have indicated a half-time of about 325 days after inhalation exposure to beryllium oxide (Sanders et al., 1975, 1978). About 25 percent of beryllium cleared from the lungs was translocated to regional lymph nodes (Sanders et al., 1978).

It is not known in detail how retained beryllium is stored in the lungs. It is likely that soluble beryllium compounds will be transformed to insoluble complexes with, for instance, phosphate, when the beryllium concentration is above a certain level (Reeves and Vorwald, 1967). Beryllium particles in the insoluble state will likely be taken up by the macrophages as demonstrated *in vitro* (Hart and Pittman, 1980). At high *in vitro* and *in vivo* exposures, beryllium has been shown to be very toxic to alveolar macrophages (Camner et al., 1974; Sanders et al., 1975).

Zorn et al. (1977) subjected rats and guinea pigs to a nasal exposure of beryllium sulfate aerosol, with ^{7}Be added as the chloride, for a period of three hours. The average deposition of ^{7}Be was reported to be 5.6 ng, which suggests that the total uptake of beryllium might have been 1624 μg. Clearance from the lungs must have been rapid since 13.5, 60, and 10 percent of the retained dose was in the skeleton, lungs, and excreta, respectively, by the end of the three-hour exposure period. Animals were killed at 20, 48, 64, 72, 96, 144, and 408 hours after exposure. During the first 5 days, there was a rapid clearance from the lungs, and after a week only 2 percent of the dose remained in the lungs. At approximately 17 weeks, the retained dose decreased to about 1.5 percent. Unfortunately, the authors did not provide information on the number of animals in each test group or on the number of animals killed at each of the designated time intervals.

4.1.2 Gastrointestinal Absorption of Beryllium

There are no data on the absorption of beryllium compounds in human beings. Estimates from animal experiments generally show low values, <1 percent in pigs (Hyslop et al., 1943), rats (Crowley, 1949; Furchner et al., 1973), mice, monkeys, and dogs (Crowley, 1949; Furchner et al., 1973). The latter studies were done using tracer amounts of ^{7}Be. Reeves (1965) gave two groups of rats, four in each group, beryllium sulfate in drinking water, the average daily intake being about 6.6 and 66.6 μg Be, respectively. In each group, one rat was killed after 6, 12, 18, and 24 weeks of exposure. Reeves found that 60-90 percent of the ingested beryllium was eliminated via feces, indicating a relatively high absorption. However, the total amount of beryllium in the skeletons from the four rats exposed to 6.6 μg/day was the same as in the skeletons from the four rats exposed to 66 μg/day, being on the average 1.49 and 1.19 μg, respectively. This suggests either that the relative absorption was much less in the high exposure group or that the uptake in bone was independent of absorbed dose. If it is assumed that 50 percent of absorbed beryllium goes to the skeleton and that the biological half time in the skeleton is 1000 days, the daily absorbed amount would be around 40 ng, i.e. about 0.6 percent of the oral daily dose.

In his reporting of the study, Reeves (1965) discussed the possibility that at the high exposure level, beryllium might be precipitated as the hydroxide as well as the phosphate. However, he goes on to reject this possibility based on the finding that the absorption rate calculated from fecal elimination data was similar in the two groups of rats. This rejection ignores the fact that the skeleton data do support the theory that the absorption rate of beryllium might be dose-dependent.

Morgareidge et al. (1977) claimed that uptake in bone was dose-dependent when rats were orally exposed to beryllium at concentrations of 5, 50, and 500 mg/kg feed for up to two years. Unfortunately, no quantitative data are given in the abstract discussing this study.

4.1.3 Percutaneous Absorption of Beryllium

There are no data on skin absorption in human beings. Tracer studies showed that small amounts may be absorbed from the rat tail (Petzow and Zorn, 1974). Belman (1969) reported that ionic beryllium applied to the skin will bind to epidermal constituents, mainly alkaline phosphatase. However, the chemical properties of beryllium make it unlikely that any significant absorption can occur through intact skin.

4.1.4 Transplacental Transfer of Beryllium

In a study by Bencko et al. (1977), the soluble salt of beryllium, $BeCl_2$, was evaluated for its ability to penetrate the placenta and reach the fetus of ICR SPF mice. Radiolabelled $^7BeCl_2$, injected into the caudal vein of 7 to 9 mice, did cross the placenta and was deposited in various organs of the fetus (see Chapter 5 for detailed discussion of this study).

No other data are available on placental transfer of beryllium.

4.2 TRANSPORT AND DEPOSITION OF BERYLLIUM IN MAN AND EXPERIMENTAL ANIMALS

Beryllium absorbed from the gastrointestinal tract will distribute mainly to the skeleton (Reeves, 1965; Mullen et al., 1972). Some beryllium has been found in the liver, but other organ concentrations have been reported to be very low (Reeves, 1965).

After injection of radioactive beryllium compounds, the highest concentrations have been found in bone and liver of rats (Hard et al., 1977) and cows (Mullen et al., 1972). The physicochemical state of the injected compound determines the main site of deposition; soluble beryllium rapidly distributes to the skeleton, whereas colloidal forms of beryllium mainly go to the liver (Klemperer et al., 1952). In rat blood, large doses of injected beryllium tend to aggregate and bind to phosphate, whereas small doses result in relatively more beryllium being in a diffusible form (Vacher and Stoner, 1968a,b). At low doses of beryllium, the main binding in human blood has been reported to be the prealbumin and α-globulin fractions of plasma (Stiefel et al., 1980). Recent data indicate that there is a binding site for beryllium in the lymphocyte membrane (Skilleter and Price, 1984).

Witschi and Aldridge (1967) studied the dose-dependence of this effect in rats. They found that less than 10 percent of the intravenous doses of beryllium sulfate (0.75-15 μg ^{7}Be/kg b.w.) was in the liver after 24 hours, whereas more than 25 percent was found in the liver following the administration of doses of 63 μg/kg b.w. or higher. They also found that with increasing dose more beryllium was found in the nuclear fraction and relatively less in the supernatant when the subcellular fractions of the rat livers were examined. At the lowest exposure (0.75 μg), the light mitochondrial fraction had the highest amount of beryllium and some evidence was presented for beryllium being located in the lysosomes. Further evidence for a role of lysosomes in hepatic accumulation of beryllium has been presented by Skilleter and Price (1979).

There are few data on beryllium levels in human beings. Analysis of tissues from people occupationally exposed to beryllium showed that, generally, the concentrations were highest in bone, liver, and kidney (Tepper et al., 1961). Meehan and Smythe (1967) reported that in the brain, kidney, spleen, liver, muscle, and heart, the concentrations were generally less than 1 μg/kg wet weight. However, in one bone sample, the concentration was 2 μg/kg, and in five vertebrae, the mean was 3.6 μg/kg. The form in which beryllium is stored in bone is presently unknown. At low exposure to beryllium, it may be bound to prealbumin and α-globulin fractions in plasma (Stiefel et al., 1980).

4.3 EXCRETION OF BERYLLIUM IN MAN AND ANIMALS

In rats given intravenous injections of tracer doses of ^{7}Be, 15 and 64 percent of the doses were excreted, via urine, 1 and 64 days after dosing, respectively (Crowley et al., 1949). In mice, monkeys and dogs, urinary excretion was the main elimination route the first days after parenteral dosing; however, later, excretion via the gastrointestinal tract equaled that of urinary excretion (Furchner et al., 1973). In early studies, Scott et al. (1950) discovered that increasing the dose in experimental animals resulted in lowering urinary excretion rates. Biliary excretion seems to play a minor role in total beryllium excretion (Cikrt and Bencko, 1975).

The biological half-time of beryllium administered via intravenous and intraperitoneal injections has been found to consist of three components, the long-term component being 1270, 1210, 890, and 770 days in dogs, mice, rats, and monkeys, respectively (Furchner et al., 1973).

After oral dosing, Reeves (1965) found that less than 1 percent of the administered dose was excreted in urine of rats.

Quantitative data on excretion of beryllium in humans are scarce. Very small amounts of beryllium (<0.1 μg/l), measured by emission spectroscopy, were found in urine from non-exposed persons (Lieben et al., 1966). Much higher values (averages of 0.9 μg/l) were reported in 120 people from California (Grewal and Kearns, 1977) and 20 individuals from Germany (Stiefel et al., 1980). In both the above studies, flameless atomic absorption spectroscopy was used to measure the beryllium concentrations. The differences observed between these two studies and that of Lieben et al. may have been due to differences in the accuracies of the analytical methods used.

Since human dietary intake of beryllium is low and animal studies suggest that gastrointestinal absorption would be low, total human body burden is likely quite low and, therefore, only a few nanograms of beryllium would be expected to be excreted daily. Based on the limited data reported by Meehan and Smythe, the soft tissue burden of an adult will likely be less than 20 μg and the skeletal burden will be about 30 μg.

Presently, no estimates exist of the biological half-time of beryllium in humans. Limited evidence suggests that the half-time in bone is likely to be many years.

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5. BERYLLIUM TOXICOLOGY

The following chapter discusses the non-mutagenic/carcinogenic effects of exposure to beryllium. Because of the greater volume of information available regarding the mutagenic and carcinogenic effects of beryllium, these topics have been discussed in the following chapters.

5.1 ACUTE EFFECTS OF BERYLLIUM EXPOSURE IN MAN AND ANIMALS

5.1.1 Human Studies

Acute lung disease from excessive exposure to beryllium compounds was first reported in the 1930's in Europe. The first U.S. case was reported in 1943 (Van Ordstrand et al., 1943). In the 1940's, many hundreds of cases occurred, but today, with improved working conditions, acute beryllium poisoning is uncommon.

Acute lung disease has been caused by inhalation of soluble beryllium compounds, e.g., the fluoride with acidic pH or the oxide, and the symptoms have been nonspecific with chemical pneumonitis as the most severe manifestation (Freiman and Hardy, 1970; Reeves, 1979). In a study of six fatal case reports, Freiman and Hardy (1970) reported that death occurred between 17 days and 10 weeks after exposure. Interstitial edema and cellular infiltration dominated the histological tissue analyses. The beryllium concentrations in the lung ranged from 4 to 1800 μg/kg.

In most cases of acute poisoning, recovery is slow, taking several weeks or months (Reeves, 1979). In the U.S. Beryllium Case Registry (BCR), a file on reported cases of acute and chronic beryllium disease, 215 cases of acute poisoning were registered up to 1967 (Freiman and Hardy, 1970). Since that time, an additional 9 cases, as of 1983, have been reported (Eisenbud and Lisson, 1983).

That there still is an occupational risk for acute beryllium disease is shown by a recent case report by Hooper (1981). An 18-year-old man involved in sandblasting and exposed to grinding dyes containing a copper-beryllium alloy developed acute respiratory disease. Open lung biopsy, six days after exposure, showed interstitial pneumonitis and slightly elevated beryllium concentrations in the lung tissue (28 μg/kg dry weight compared to normal levels of <20 μg/kg).

Acute skin effects in the form of contact dermatitis after contact with soluble beryllium salts have been described (Van Ordstrand et al., 1945).

5.1.2 Animal Studies

Acute chemical pneumonitis has been produced in a great variety of animals exposed to beryllium sulfate or fluoride (Stokinger et al., 1950). Some insoluble compounds, especially low-fired beryllium oxide, have also caused acute effects in rats (Hall et al., 1950). The concentrations needed to cause acute effects have generally been on the order of several mg/m^3.

Injection of beryllium compounds can cause acute liver damage (Cheng, 1965; Aldridge et al., 1950).

5.2 CHRONIC EFFECTS OF BERYLLIUM EXPOSURE IN MAN AND ANIMALS

5.2.1 Respiratory and Systemic Effects of Beryllium

5.2.1.1 Human Studies--The fact that beryllium can cause chronic lung disease was first reported by Hardy and Tabershaw in 1946. They presented data on 17 persons employed in the fluorescent lamp manufacturing industry. The main symptoms noted were dyspnea on exertion, cough, and weight loss. In most cases the symptoms first appeared several months or even years after the last exposure. The patients were generally young, below 30 years of age, and the majority were women. X-ray examinations and autopsy findings provided additional information. The X-rays showed that an early sign of chronic beryllium poisoning was a fine diffuse granularity in the lungs. In the second stage, a diffuse reticular pattern was also seen, and in the third stage, distinct nodules could be seen. Histological examination of the lungs in an autopsy case showed a granulomatous inflammation characterized by central and eccentrically located giant cells of the foreign body type in the alveoli. Infiltration of plasma cells and lymphocytes was another feature. After generally less than two years of illness, five deaths occurred among the 17 persons. In a couple of cases, some recovery was noted and in some other cases persistent disability occurred.

This pioneer study of chronic beryllium disease led to further studies which have been documented in papers by Hardy (1980) and Eisenbud (1982). In addition to further cases of occupational beryllium poisoning, there have also been reports on "neighborhood cases," i.e., beryllium disease in persons living in the vicinity of beryllium-emitting plants. In these cases, exposure has not only been to beryllium in ambient air, but also to contaminated clothing brought into the house from occupationally exposed members of the household (Eisenbud et al., 1949). At least 3 children, ages 7-14 years, have been among these cases (Hall et al., 1959).

These findings and the experience from acute beryllium poisoning led to the initiating of beryllium standards in both the industrial and general environment. To prevent acute disease, a TLV of 25 $\mu g/m^3$ was proposed in 1949 as a maximum permissible peak occupational exposure during 30 minutes, and a level of 2 $\mu g/m^3$ was set as an average 8-hour exposure. For the general environment, a level of 0.01 $\mu g/m^3$ was proposed. It should be noted that the 2 $\mu g/m^3$ standard was, in fact, not based on actual dose-response relationships. As stated by Eisenbud (1982), this was a standard based on the molar toxicity of beryllium in relation to some heavy metals like lead and mercury, with TLVs around 100 $\mu g/m^3$.

While these proposed standards seemed to prevent acute poisoning, during the following years, many new cases of chronic beryllium disease were discovered, mainly as a result of heavy exposures in the years 1940 to 1946. This led to the foundation of the previously mentioned Beryllium Case Registry in 1952. The intention of the Registry was that it would serve as a file for all cases of acute and chronic beryllium disease, from which information on the development and clinical manifestations of beryllium disease could be obtained. Since 1978, the Registry has been maintained by the National Institute for Occupational Safety and Health.

Throughout the years, many scientific reports have appeared based on the information in the Registry. In 1959, Hall et al. presented some data on 601 persons who at that time (1959) had entered the registry. As seen in Table 5-1, the majority of male cases in 1959 were acute, but in later reports the number of chronic disease cases increased and now number more than 600 in total, whereas only a few more cases of acute disease have been reported. It should be noted that 28 of the acute cases in Table 5-1 were also classified as chronic. In 1966-1974, 74 new cases were reported to the BCR, of which 36 had been exposed after 1949 (Hasan and Kazemi, 1974).

Typical of chronic beryllium disease is that it may appear many years after cessation of exposure. In Table 5-2, it can be seen that the time since last exposure in more than 20 percent of the cases reported up to 1959 was more than 5 years, the maximum being 15 years. There has been some overlapping between

TABLE 5-1. BERYLLIUM REGISTRY CASES, 1959

	Men	Women	Total	Dead
Acute	227	20	247 (39%)	15 (6%)
Chronic	191	191	382 (61%)	121 (31%)

Source: Hall et al. (1959)

TABLE 5-2. TIME FROM LAST EXPOSURE TO FIRST SYMPTOM* IN THE BCR, 1959

Time	Cases of beryllium disease	%
Less than 1 month	126	41
1 month to 1 year	27	9
1-5 years	89	29
5-10 years	56	18
More than 10 years	12	4
	310	

*Maximum was 15 years.

Source: Hall et al. (1959)

acute and chronic disease, but generally the disease has been registered as chronic if it has lasted more than one year.

In the latest report, 897 cases have been registered in the BCR, 10 of which have been added since 1978 (MMWR, 1983). Eisenbud and Lisson (1983) reported on 888 cases, but mentioned that they knew about 45 chronic cases which had not been included as of their report. Therefore, the total number of cases may well be over 900.

Of the 888 cases reported by Eisenbud and Lisson, 224 were classified as acute. This number is smaller than the one given in Table 5-1, but as mentioned earlier, 28 acute cases in that table were also classified as chronic. The chronic cases were reported to be 622, leaving 42 cases unaccounted. Of the 622 cases, 557 occurred in individuals occupationally exposed and 65 occurred among members of the general populace. Of the latter, 42 were attributed to ambient air exposure and 23 to dust exposure in the homes.

The majority of the occupational cases were either from exposures within the fluorescent lamp industry (319) or within beryllium extraction plants (101). In 62 percent of the occupational cases, dates for first exposure and onset of disease were available. Figure 5-1 shows that latency times may have been up to 40 years, but have been declining in recent years. Eisenbud and Lisson acknowledged that caution should be exercised in interpreting the data in Figure 5-1, as a rough correspondence between the maximum latency time and number of years elapsed since first exposure must exist. Thus, it could be argued that cases with longer latencies will develop among more recent cohorts in later years. While the authors disputed this argument by noting that reduction in maximum latency paralleled the reduction in mean latency, which also declined through time (Table 5-3); nevertheless, it is clear that a person exposed in 1960 cannot, by the end of the study period, have a latency time of more than 20 years.

Some of the most common symptoms of chronic beryllium disease are shown in Table 5-4 (Hall et al., 1959). These symptoms confirm what was earlier reported by Hardy and Tabershaw in 1946. Table 5-5 shows some of the signs of chronic beryllium disease. The cardiovascular signs can be attributed to the cor pulmonale, which is a sequela to the severe forms of chronic beryllium disease. There are also some other signs which may be seen as pure systemic effects of beryllium exposure.

An extensive description of chronic beryllium disease was presented by Stoeckle et al. (1969). In that paper, mainly clinical and X-ray findings and results of treatment were presented. In another paper by Freiman and Hardy (1970), the pulmonary pathology was presented. In the paper by Stoeckle et al., data were shown on 60 patients with chronic beryllium disease, who had been investigated at the Massachusetts General Hospital between 1944 and 1966. This group came from different industries and no data were presented on exposure levels, so the data cannot be used for any dose-response estimations. However, valuable information was given on the clinical findings and the diagnostic problems encountered in the examination of these patients. In addition to the pulmonary effects, there was further evidence for extrapulmonary signs of beryllium disease. In some patients, granulomas were found in muscle or skin.

Some of the features of chronic beryllium disease are similar to those seen in sarcoidosis. In the paper by Stoeckle et al., as well as in an earlier paper by Israel and Sones (1959), the differentiation of these two diseases is

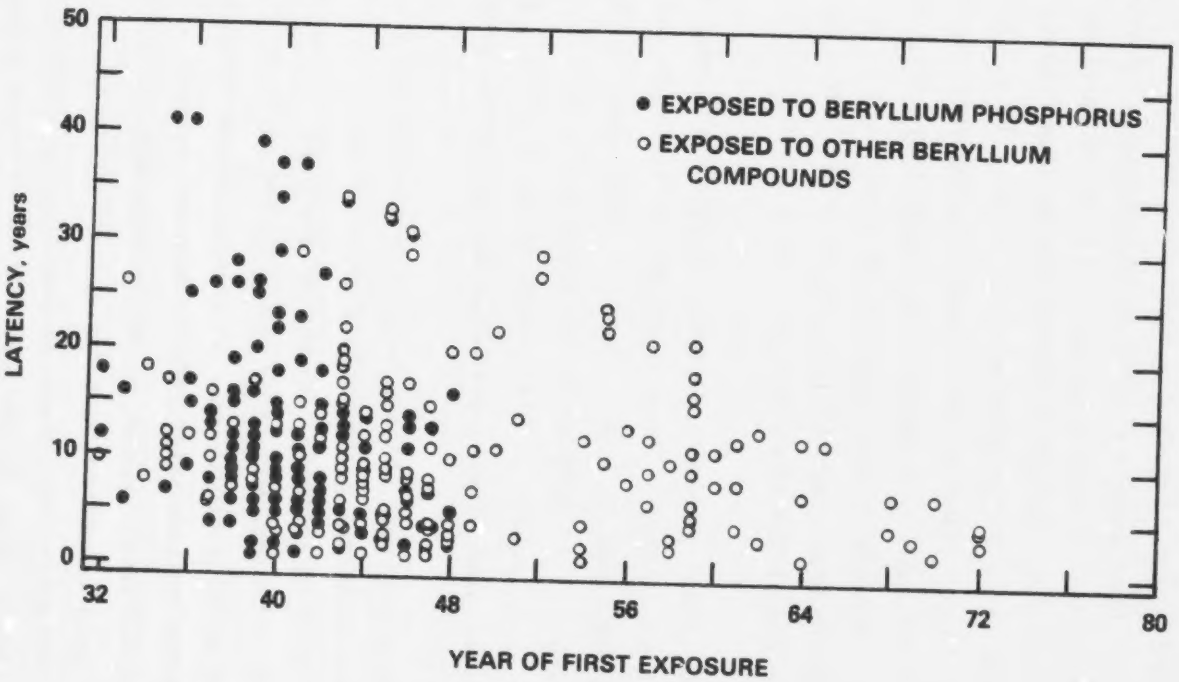


Figure 5-1. Latency according to year of first exposure (occupational berylliosis).

Source: Eisenbud and Lisson (1983).

TABLE 5-3. CHANGES OF LATENCY FROM 1922 TO PRESENT IN OCCUPATIONAL BERYLLIOSIS CASES

Period of First Exposure	No. of Cases	Latency, yr	
		Mean	Range
1922-1981	347*	11	1-41
1922-1937	33	16	4-40
1938-1949	264	9.8	1-39
1950-1959	32	9.6	1-25
1960-1981	18	6.6	1-13

*Cases were included only if both dates of first exposure and diagnosis of first symptoms were known; 62 percent of all chronic cases reported to the Registry were included.

Source: Eisenbud and Lisson (1983).

TABLE 5-4. SYMPTOMS OF CHRONIC BERYLLIUM DISEASE

Symptom	%
Dyspnea	
on exertion	69
at rest	17
Weight loss	
more than 10%	46
0% to 10%	15
Cough	
nonproductive	45
productive	33
Fatigue	34
Chest pain	31
Anorexia	26
Weakness	17

Source: Hall et al. (1959)

TABLE 5-5. SIGNS OF CHRONIC BERYLLIUM DISEASE*

Sign	%
Chest signs	43
Cyanosis	42
Clubbing	31
Hepatomegaly	5
Splenomegaly	3
Complications	
Cardiac failure	17
Renal stone	10
Pneumothorax	12

*Signs are not included when they are attributable to cardiac failure.

Source: Hall et al. (1959)

discussed. The main difference is that in sarcoidosis there is much more systemic involvement, as noted in more than 80 percent of the cases. X-ray of the lungs may, however, show very similar pictures.

Among laboratory findings in cases of beryllium disease, hypercalcemia, hypercalcuria, stone formation, and osteosclerosis have been noticed (Stoeckle et al., 1969) as has hyperuricemia (Kelley et al., 1969).

In addition to the studies based on the BCR, there have also been some studies within industrial populations. Wagoner et al. (1980) conducted a mortality study on a cohort of 3055 workers exposed to beryllium in a plant in Pennsylvania. (See Section 7.2 for detailed discussion of lung cancer within the cohort.) Among causes of death other than lung cancer, there was a significant excess of heart disease (396 observed versus 349 expected) and respiratory disease other than influenza and pneumonia (31 observed versus 18.7 expected). It is conceivable that some of the cardiac deaths were, in fact, caused by cor pulmonale secondary to beryllium disease. There are no data that indicate that beryllium exposure via inhalation has a direct effect on the cardiovascular system.

These data can be compared to a mortality study by Infante et al. (1980) on 421 white males listed in the BCR during the period of 1952 through 1975.

Heart disease was stated to be the cause of death in 31 of these cases (29.9 were expected), whereas respiratory disease other than influenza and pneumonia was the cause of death in 52 cases (only 1.6 were expected).

Recently, it has been suggested that beryllium exposure may cause granulomas in different parts of the body which may prove fatal when the myocardium is affected. Hözberg and Rajs (1980) reported granulomatous myocarditis as the cause of death in two individuals occupationally exposed to beryllium.

Results of studies on respiratory function have been presented by Andrews et al. (1969), Kanarek et al. (1973), and Sprince et al. (1978). Andrews et al. performed lung function tests, e.g., vital capacity and FEV_1, on 41 patients from the BCR with chronic beryllium disease. Only in two patients were the test results normal; 16 out of the 41 patients had airway obstruction.

The studies by Kanarek et al. and Sprince et al. were performed on workers employed in beryllium extraction and processing plants. In the first study, 214 employees were examined. They had been exposed for 1 to 14 years and exposure had started after recommended occupational standards had been set. It was known, however, that the recommended standards of 2 and 25 $\mu g/m^3$ for 8-hour and short-term exposures, respectively, had been exceeded. In some areas of the plants peak exposures were above 1 mg/m^3. A large number of lung function tests were performed, including FVC, FEV_1, and gas exchange. Among 31 subjects with X-ray abnormalities of the lung, there were 11 with hypoxemia at rest, but these subjects were also heavy smokers. In this study, there was no control group and it is, therefore, difficult to establish to what extent smoking or beryllium caused some of the effects. However, in two subjects, lung biopsies were performed, and in one of these cases a diffuse granulomatous reaction, typical for beryllium exposure, was found. In both cases the beryllium content of the lung was elevated. It is noteworthy that the case with granulomatous reaction had much lower beryllium concentrations in the lung tissue than the case without tissue changes.

A follow-up was made 3 years later on these workers, as reported by Sprince et al. (1978). Exposure levels were now much lower due to new engineering, and peak concentrations were now less than 25 $\mu g/m^3$. For some operations, peak concentrations were even less than 2 $\mu g/m^3$. One hundred eleven workers who had participated in 1971 and had not changed smoking category were studied

(Table 5-6). There were no major differences between the results from the two examinations, but as seen in Table 5-7, there had been some improvement of hypoxemia as indicated by the results of the Pa_{O_2} determinations. In the 13 persons who had clearly demonstrated hypoxemia in 1971, there was a highly significant rise--on an average, 19 mm higher--in Pa_{O_2} in 1974. Among the 98 workers who had normal Pa_{O_2} in 1971, the average increase was 4.1 mm. Of the 31 subjects who had X-ray abnormalities in 1971, nine now showed normal X-ray readings. These findings indicate that some minor changes might be reversible in beryllium-exposed workers, if exposure is reduced. A new follow-up was conducted in 1977 and briefly reported (Sprince et al., 1979). The improvement in Pa_{O_2} remained and there was a tendency towards normalization of lung X-rays. It is obvious, however, that, due to long latency times, longer follow-ups are necessary before any final conclusions can be made with regard to prognosis.

In addition to the U.S. studies, studies have been conducted in other countries on workers exposed to beryllium (Cotes et al., 1983; Bencko et al., 1980).

In a recent British study, Cotes et al. (1983) presented data on workers exposed to beryllium compounds, mainly beryllium oxide. The plant in which these workers had been employed started operation in 1952. The first study of these workers was made in 1963 when 130 men out of a group of 146, who had worked for more than 6 months, were examined. Chest X-rays were taken and, in all but one case, pulmonary function was measured by a set of respiratory function tests. In a follow-up in 1973, 106 of the 130 were examined. In another follow-up in 1977, only 8 men from that group and one ex-employee were examined, but to this new group were added 24 employees and 14 ex-employees employed since 1963. The same tests were performed on these subjects.

Airborne beryllium had been measured during the years 1952 to 1960, but no measurements seemed to have been made since 1960. In a total of 3401 samples taken, only 20 exceeded the 25 $\mu g/m^3$ limit and 318 exceeded the 2 $\mu g/m^3$ limit. Mean concentrations were presented as geometric means, and in both 1952 and 1960 these concentrations were never above 2 $\mu g/m^3$. Generally, concentrations were far below 1 $\mu g/m^3$. The 1963 study found 6 cases of definite or suspected beryllium disease. The follow-up studies did not find any new cases. However, after the 1977 study, two further cases were added. Both were men who had worked since 1952. There were also two cases of acute

TABLE 5-6. COMPARISON OF 1971 AND 1974 DATA OF WORKERS SURVEYED IN BERYLLIUM EXTRACTION AND PROCESSING PLANTS*

Workers	Year	No.	Age (years)	Cigarette-Pack-years	Length of Employment (years)	FEV_1 (% predicted)	FVC (% predicted)	PEFR (% predicted)
Smokers	1971	55	40.9	23	10.2	92.9	96.6	96.9
	1974	55	43.9	27	13.2	90.4	95.2	$91.3^{\dagger}$ $(P < 0.02)$
Ex-smokers	1971	36	43.3	25	10.6	97.9	97.8	100.0
	1974	36	46.3	25	13.6	97.7	101.2	$94.8^{\dagger}$ $(P = 0.02)$
Nonsmokers	1971	20	43.4	0	10.9	105.3	98.6	104.7
	1974	20	46.4	0	13.9	102.4	102.5	99.2
Total	1971	111	42.1	23.5	10.4	96.7	97.3	99.3
	1974	111	45.1	26.2	13.4	95.1	98.5	$93.8^{\dagger}$ $(P < 0.01)$

Definition of abbreviations: FEV_1 = 1-sec forced expiratory volume; FVC = forced vital capacity; PEFR = peak expiratory flow rate.

*Results are mean values.

†Significant difference, comparing results in 1971 with those in 1974.

Source: Sprince et al. (1978)

TABLE 5-7. COMPARISON OF 1971 AND 1974 ARTERIAL BLOOD GAS RESULTS*

Workers	Year	No.	Pa_{O_2} (mm Hg)	Pa_{CO_2} (mm Hg)	pH
Smokers	1971	55	90.9	38.0	7.42
	1974	55	$96.1^{\dagger}$	$35.1^{\dagger}$	7.42
Ex-smokers	1971	36	89.1	37.9	7.42
	1974	36	$95.7^{\dagger}$	$36.1^{\dagger}$	7.42
Nonsmokers	1971	20	93.4	38.0	7.43
	1974	20	100.2^{**}	36.3	$7.41^{\dagger}$
Total	1971	111	90.8	38.0	7.43
	1974	111	$96.8^{\dagger}$	$35.7^{\dagger}$	7.42^{**}

Definition of abbreviations: Pa_{O_2} = arterial P_{O_2}; Pa_{CO_2} = arterial P_{CO_2}

*Results are mean values.

$^{\dagger}P < 0.01$, comparing 1971 with 1974 results.

$^{**}P < 0.05$, comparing 1971 with 1974 results.

Source: Sprince et al. (1978)

beryllium pneumonitis, and these two men were among a group of 17 who were deemed to have had the highest exposures. Both these cases were normal in the 1963 study.

After adjusting for age, smoking, and other personal attributes, the respiratory function tests only showed that exposure was related to large vital capacity. In the 1963 study, a significant negative correlation between estimated total exposure to beryllium and lung compliance was shown in a subgroup of 19 workers from the slip-casting bay. Comparison between data from 1963 and 1973 showed only changes that could be ascribed to personal attributes. The conclusion of the authors was that respiratory function studies generally could not detect beryllium disease before radiographic changes appeared. Decreases in lung function were only observed in cases with clear X-ray changes. However, Preuss and Oster (1980) have noted that changes in vital capacity may occur long before X-ray changes appear.

As mentioned above, chronic beryllium disease differs from some other occupational lung diseases, in that it also has a systemic component. The systemic involvement suggests that there is also an immunological component to the disease and that hypersensitivity can explain some of the findings in chronic beryllium disease.

In 1951, Curtis developed a patch test, which was found to be positive for most cases of dermatitis and skin granuloma caused by beryllium. In addition, it was found to be positive in many cases of lung disease caused by beryllium (Curtis, 1959) and in beryllium-exposed workers (Nishimura, 1966). However, it was also found that the patch test could initiate the development of skin reactions or pulmonary disease in people exposed to beryllium, but who had not had previous symptoms of respiratory illness (Sneddon, 1955; Stoeckle et al., 1969; Rees, 1979; Cotes et al., 1983).

Recently, attempts have been made to develop other tests suitable for studying hypersensitivity to beryllium. The lymphocyte transformation test, as reported by Williams and Williams (1982a,b, 1983), is deemed to be the most useful. This test gave a positive response in 16 patients with established chronic beryllium disease, whereas it was negative in 10 subjects with suspected disease. Only two positive responses were reported among 117 healthy beryllium workers (Williams and Williams, 1983). It is not clear, however, if a positive test in an otherwise healthy worker really indicates that such an individual is at a higher risk for getting pulmonary disease.

In an area in Czechoslovakia where coal with a high beryllium content is burned, Bencko et al. (1980) studied immunoglobulins and autoantibodies both in workers in a power plant and in people living in the vicinity of the plant. The concentration of beryllium in the town was estimated to be, on an average, 80 ng/m^3, which is 8 times higher than the suggested standard for ambient air in the U.S. In both the workers and general public, elevated levels of immunoglobulins IgG and IgA and increased concentrations of autoantibodies were found, compared to a control group not exposed to beryllium. The workers had higher exposure than the town dwellers, up to 8 μg/m^3, and they also had considerably higher levels of IgM than the town residents or the control group. Since many factors can contribute to increases in immunoglobulin levels, the significance of these findings is not clear.

5.2.1.2 Animal Studies--There have been a large number of animal studies on the chronic effects of beryllium exposure via air. Much of the early work in the 1940's and 1950's has been described by Vorwald et al. (1966). A large number of studies on the rat were performed by Vorwald and co-workers, but many of these studies have never been fully reported and the main data base remains the 1966 review by Vorwald and co-workers.

In one study, rats were exposed to beryllium sulfate aerosol in concentrations ranging from 2.8 to 194 μg/m^3 of air. The exposures were usually given 7 hours a day, for 1 to 560 days. It was stated that exposure to 2.8 μg/m^3 did not produce any specific inflammatory abnormalities, whereas 21 μg/m^3 caused significant inflammatory changes in some long-surviving rats. Forty-two μg/m^3 produced chronic pneumonitis and 194 μg/m^3 caused acute disease.

The main finding of this study was that the low-exposure group had a high incidence of pulmonary cancer, 13 of 21 rats. There has been some concern about the validity of the low-exposure data, however (see Section 7.1.8.3). In the group exposed to 42 μg/m^3, microscopic examination of lung tissue showed alveolar changes with a large increase in macrophages. With longer exposure, diffuse pneumonitis and focal granulomatous lesions became increasingly prominent, typically occurring in patches.

Schepers et al. (1957) exposed rats to beryllium sulfate; the average concentration of beryllium was about 35 μg/m^3. In one experiment 21 animals were exposed for 1 to 30 days; in another experiment 115 animals were exposed for 6 months. The number of controls was 17 and 69, respectively. In the latter study, 46 animals out of the 115 died during exposure and 29 were killed at the end of exposure. Fifty-two rats were then transferred to normal air and observed for up to 18 months after cessation of exposure. The cause of death during exposure was mainly pleural pericarditis with a tendency to chronic pneumonitis. No bacteria were isolated, but the authors concluded that this response was caused by infection, since sulfathiazole had a beneficial effect. In further experiments, similar exposures were given and no rats died during exposure or up to 9 months following exposure. Among the findings after 6 months of exposure were neoplastic changes, foam-cell clusters, focal mural infiltration, lobular septal cell proliferations, peribronchial alveolar wall epithelialization and granulomatosis.

In a study by Reeves et al. (1967), 150 rats (same number of controls) were exposed to beryllium sulfate at a mean concentration of 34 $\mu g/m^3$. Exposure was for 72 weeks, 7 hours/day, 5 days/week. Variations in the exposure concentrations must have been large (some above 100 $\mu g/m^3$) since the standard deviation was reported to be about 24 $\mu g/m^3$. Every month, 3 male and 3 female rats from the exposed and control groups were killed. Among the findings were progressive increases in lung weight in the exposed animals. At the end of the experiment, the lung weights of exposed animals were, on an average, more than four times greater than those of controls. Histological examination showed inflammatory and proliferative changes. Also, clusters of macrophages in the alveolar spaces were a common finding. Granulomatosis and fibrosis were only occasionally seen. The proliferative changes ultimately led to a large number of tumors in the exposed animals (see Section 7.1.1).

Wagner et al. (1969) exposed two groups of 60 rats each to the beryllium ores, beryl and bertrandite. Exposure was for up to 17 months to 15 mg/m^3 of the ores, corresponding to 210 μg beryllium/m^3 as bertrandite and 620 $\mu g/m^3$ as beryl. Exposure was generally for 6 hours/day, 5 days/week. A very large incidence of lung tumors was reported. Among the non-malignant changes, study clusters of macrophages were seen. Granulomas were seen in lungs from bertrandite-exposed rats.

The last major study on the rat seems to be the study by Sanders et al. (1975). They exposed rats to beryllium oxide particles calcined at 1,000°C. Exposure to the beryllium oxide was via the nose only and all exposures were single. Exposures ranged from 30 to 180 minutes and concentrations of beryllium were from 1 mg to 100 mg/m^3. The single exposures resulted in chronic changes characterized by the appearance of foamy macrophages and some granulomatous lesions. A significant depression of alveolar clearance was observed.

Other animal studies have examined the effects of beryllium exposure on monkeys (Vorwald et al., 1966; Schepers, 1964; Conradi et al., 1971), dogs (Conradi et al., 1971; Robinson et al., 1968), guinea pigs (Policard, 1950; Reeves et al., 1971, 1972) and hamsters (Wagner et al., 1969).

Vorwald et al. (1966) exposed monkeys to intermittent daily administrations of beryllium sulfate (average concentration of 35 $\mu g/m^3$) for several months. Some monkeys were given intratracheal instillations of beryllium oxide. Both routes of administration led to typical chronic beryllium disease with pneumonitis and granulomatosis.

Schepers (1964) exposed three groups of monkeys, 4 in each group, to aerosols of beryllium fluoride, beryllium sulfate, and beryllium phosphate in concentrations of about 200 $\mu g/m^3$ as beryllium. In another experiment, two groups of monkeys, 4 animals in each, were given higher concentrations of the beryllium phosphate, about 1140 and 8380 $\mu g/m^3$ of beryllium, respectively. Exposure was 1 or 2 weeks in the animals exposed to the fluoride and sulfate, and from 3 days to 30 days in the groups exposed to the phosphate. After exposure ceased, the animals were kept in normal air for different periods of time.

There were signs of initial general toxicity, in the form of anorexia, in the exposed animals. Dyspnea, one of the typical signs of human chronic beryllium disease, developed rapidly in the animals exposed to fluoride and to the high beryllium phosphate concentrations. After cessation of exposure, some recovery was noted. Mortality was 100 percent in the animals exposed to the two highest phosphate concentrations. Examination of lungs from animals who either died during the experiment or were killed showed pulmonary edema and congestion, mainly in the animals exposed to the fluoride and to the highest phosphate concentration. Cor pulmonale was also a common finding. The histological picture was similar to what has been seen in other experimental animals and in human beings. Notable were pigment-filled macrophages and invasion of plasma cells in the alveoli.

Wagner et al. (1969) exposed 2 groups of 12 squirrel monkeys each, for 23 months, to beryl and bertrandite dust under the same exposure conditions as described for rats. While both dusts caused macrophage clusters, no other marked changes were seen compared to the controls.

The effects of beryllium oxide calcined at 1400°C were studied by Conradi et al. (1971). Five monkeys received inhalation exposures with concentrations varying between 3.3 and 4.4 mg beryllium/m^3. Exposure was for 30 minutes at 3 monthly intervals; the animals were observed for 2 years and then killed. The results of histological examinations were essentially negative. No major differences could be seen between controls and exposed animals.

Conradi et al. also studied 6 dogs exposed in the same way as the monkeys. No pathological changes were observed in the dogs.

Robinson et al. (1968) gave much higher doses of beryllium to dogs. Two dogs were exposed for 20 minutes to rocket exhaust products containing mixtures of beryllium oxide, beryllium fluoride and beryllium chloride at average concentrations of 115 mg beryllium/m^3. The dogs were observed for a period of 3 years, and then killed. Immediately after exposure the dogs had some acute symptoms, but during the rest of the study they remained clinically healthy. Histological examination of the lungs showed small foci of granulomatous inflammation scattered throughout the lungs of both dogs. Beryllium deposits were also found in the lungs. The average beryllium content of the lungs of these 2 dogs was 3.9 and 5.5 mg/kg wet weight, respectively.

Granulomatosis has also been shown in guinea pigs exposed to beryllium oxide dust (Policard, 1950; Chiappino et al., 1969). In the guinea pig, it has been possible to produce beryllium sensitivity, and this seems to have some protective effect against the development of pulmonary disease (Reeves et al., 1971; Reeves et al., 1972). Barna et al. (1981) studied two strains of guinea pigs given intratracheal injections of 10 mg of beryllium oxide. All of the animals in one strain developed lung disease, whereas the animals in the other strain did not, indicating genetic differences. The latter animals also showed negative skin tests and lymphocyte transformation tests, whereas positive reactions were seen in the group with the lung reactions. Administration of the immunosuppressive drug, prednisone, had a beneficial effect on the animals with lung disease; however, this effect only lasted as long as the treatment with the drug continued. Following cessation of the drug, the lung disease reappeared, demonstrating the persistence of beryllium in the lung.

Wagner et al. (1969) exposed two groups of hamsters, 48 animals in each group, for 17 months to beryl and bertrandite dust under the same exposure conditions previously described for rats and squirrel monkeys. After 6 months of exposure, the bertrandite-exposed animals had a few granulomatous lesions in the lungs, and, in both groups, there were some atypical cell proliferations.

Interestingly, in the various studies which have shown differing degrees of granulomatosis in rats, it is noteworthy that rats have not developed hypersensitivity to beryllium (Reeves, 1978).

There have also been some studies where animals have been orally exposed to beryllium for long periods. In some early studies (Guyatt et al., 1933; Jacobson, 1933; Kay and Skill, 1934), rickets were produced in young animals by giving large oral doses of beryllium carbonate (0.1-0.5 percent; 1000-5000 mg/kg) in the diet. This effect has since been regarded as an indirect effect due to the binding of phosphate to beryllium in the gut and phosphorus depletion in the body.

Schroeder and Mitchener (1975a,b) gave groups of male and female rats and mice beryllium in drinking water at a concentration of 5 mg/l for their respective lifetimes. No consistent differences could be noticed between exposed animals and controls with regard to weight and lifespan. In a 2-year feeding study, Morgareidge et al. (1977, abstract) fed rats dietary concentrations of 5, 50, and 500 mg beryllium/kg. The highest dose level resulted in a slight weight depression. Specific details about the results were not reported.

A large number of experiments have been conducted on beryllium compounds injected into animals. Some of these studies are mentioned in Section 7.1 on experimental carcinogenicity. The results from some of these studies have also been presented in earlier documents on beryllium, especially with regard to effects on enzymes (Drury et al., 1978). Since these exposure routes are not relevant for understanding the action of beryllium in humans, they will not be discussed further in this document.

5.2.2 Teratogenic and Reproductive Effects of Beryllium

5.2.2.1 Human Studies--No known studies have been reported concerning the teratogenic and reproductive effects of beryllium exposure in humans.

5.2.2.2 Animal Studies--Very few studies have investigated the teratogenic or reproductive effects produced by beryllium exposure of animals. The available information consists of one study evaluating the behavioral effects of offspring exposed to beryllium sulfate during pregnancy (Hirotoda and Hoshishima, 1979), a study dealing with the ability of beryllium chloride to penetrate the placenta (Bencko et al., 1979), and a study concerned with the effects of beryllium chloride on developing chick embryos (Puzanova et al., 1978).

Hoshishima et al. (1978) presented a brief abstract and, later, a more extensive report (Tsujii and Hoshishima, 1979) on the effects of trace quantities of beryllium injected into pregnant CFW strain mice. Six females per group were exposed to a total of 22 kinds of metals which included $BeSO_4$ (140 ng/mice/day). The mice received intraperitoneal injections (0.1 ml) 11 times during pregnancy. The injections were given once daily for three consecutive days and then every other day for eight treatments. The gestational days of treatment were not reported. In this study, beryllium (140 ng/day) produced the following differences in the pups exposed *in utero* as compared to the control group: delayed response in head turning in the geotaxis test, acceleration in the straight-walking test, delayed bar-holding (for a moment) response, and acceleration of bar holding (for 60 seconds).

The authors suggested that trace elements may have stimulating effects on physiological processes if given in concentrations similar to those found in nature, but if greater concentrations are given, then the effect could be irritating. However, the results of this study are too equivocal to confirm or deny this possibility. Further studies, using more than one dose level, would have to be conducted to establish this hypothesis. In addition, more basic research on the significance of the behavioral responses must be done in order to understand whether an acceleration or diminution of the various responses represents a true adverse effect.

In a study by Bencko et al. (1977), the soluble salt of beryllium, $BeCl_2$, was evaluated for its ability to penetrate the placenta and reach the fetus. Radiolabelled $^7BeCl_2$ was injected into the caudal vein of 7 to 9 ICR SPF mice and was administered in 3 different time periods: (1) before copulation (group A), (2) the 7th day of gestation (group B), and (3) the 14th day of gestation (group C). The animals were sacrificed on the 18th to 19th day of pregnancy and the radioactivity associated with the fetal and maternal compartments was evaluated. In fetuses exposed on the 14th day of gestation, higher levels of radioactivity were associated with the fetal compartment as compared to other exposure periods (group A, 0.0002 μg ^7Be/g fetus; group B, 0.0002 μg ^7Be/g fetus; and group C, 0.0013 μg ^7Be/g fetus). The amount of radioactivity in the other organs of the fetus was generally not influenced by beryllium exposure except in the spleen and liver. The amount of ^7Be penetrating the spleen was decreased, while in the liver it was increased when ^7BeCl was given on the 14th day of pregnancy.

Puzanova et al. (1978) conducted studies on the effects of beryllium on the development of chick embryos. $BeCl_2$ (300 µg to 0.00003 µg dissolved, in 3 µl twice-distilled water) was injected subgerminally into chick embryos (10 embryos per dose) on the second day of embryogenesis. After a 24-hour incubation, the eggs were opened and stained with 0.1 percent neutral red so that the distance between the origin of the vitelline arteries and the caudal tip of the body could be measured. In a second part of this experiment, the same doses of $BeCl_2$ were administered subgerminally to 2-day embryos, and intra-amniotically to 3- and 4-day embryos. The surviving embryos were examined after the 6th day of incubation.

In the first part of the experiment, it was found that 300 µg $BeCl_2$ caused complete embryolethality while 0.3 µg was not lethal to any embryos. Doses of 0.003 µg and under had no observable effect on the development of the embryos. When the eggs were treated on day 2, the most common malformation was caudal regression and open abdominal cavity and ectopia cordis. When administered on the fourth day, execephalia, mandibular malformation, and malformations described as the straitjacket syndrome were reported. It is not known, however, if these types of teratogenic effects in chick embryos are reflective of effects that might occur in humans. Additional studies would have to be done using mammals to determine whether beryllium has teratogenic potential.

Considered collectively, the available information from the above studies is not sufficient to determine whether beryllium compounds have the potential to produce adverse reproductive or teratogenic effects. It should be noted that these studies were not designed to specifically investigate the effects of beryllium compounds on reproduction or the developing conceptus. Further studies in this area would be desirable.

6. MUTAGENIC EFFECTS OF BERYLLIUM

Beryllium has been tested for its ability to cause genetic damage in both prokaryotic and eukaryotic systems. The prokaryotic systems include gene mutations and DNA damage in bacteria. The eukaryotic systems include DNA damage and gene mutations in yeast and cultured mammalian cells, and studies for chromosomal aberrations and sister chromatid exchanges in mammalian cells *in vitro*. The available literature indicates that beryllium has the potential to cause gene mutations, chromosomal aberrations, and sister chromatid exchange in cultured mammalian somatic cells.

6.1 GENE MUTATIONS IN BACTERIA AND YEAST

The studies on beryllium-induced gene mutations in bacteria and yeast are summarized in Table 6-1.

6.1.1 Salmonella Assay

Beryllium has been tested for its ability to cause reverse mutations in *Salmonella typhimurium* (Simmon, 1979a; Rosenkranz and Poirier, 1979).

Simmon (1979a) found that beryllium sulfate was not mutagenic in *Salmonella* strains TA1535, TA1536, TA1537, TA98, and TA100. Agar incorporation assay with and without S-9 metabolic activation was employed. The highest concentration of beryllium sulfate tested was 250 µg/plate (1.41 µmole). No mutagenic response was obtained in any of the above strains.

Beryllium sulfate was also not mutagenic in *Salmonella typhimurium* strains TA1535 and TA1538, both in the presence and absence of S-9 activation system (Rosenkranz and Poirier, 1979). Two concentrations of the test compound used were 25 µg/plate and 250 µg/plate. No significant differences in the mutation frequencies between the experimental and the control plates were noted.

6.1.2 Host-Mediated Assay

Negative mutagenic response of beryllium sulfate was obtained in the host-mediated assay (Simmon et al., 1979). Several procedures were used. In all procedures the tester strain was injected intraperitoneally and the beryllium sulfate was given orally or by intramuscular injection. Four hours later, the *Salmonella* or *Saccharomyces* tester strain was recovered from the

TABLE 6-1. MUTAGENICITY TESTING OF BERYLLIUM: GENE MUTATIONS IN BACTERIA AND IN YEAST

Test System	Strain	Concentration of Test Compounds	S-9 Activation System	Results	Comments	Reference
Salmonella typhimurium	TA1535 TA1536 TA1537 TA100 TA98	Maximum of 250 µg/plate	±	Reported negative in all strains	1. Only highest concentration used.	Simmon, 1979a
Salmonella typhimurium	TA1530 TA1538 TA1535	25 mg/kg i.m. 1200 mg/kg gavage	Host-mediated assay in mice	Reported negative in all strains by both routes of exposure		Simmon et al., 1979
Saccharomyces cerevisiae	D_3	1200 mg/kg gavage				
Salmonella typhimurium	TA1535 TA1538	25 µg/plate 250 µg/plate	±	Reported negative		Rosenkranz and Poirier, 1979
Escherichia coli	WP2	0.1-10 µmol/plate (0.9-90 µg/plate)		Reported negative		Ishizawa, 1979
Escherichia coli (*pol* assay)	Pol A^+ Pol A^-	250 µg/plate	±	Reported negative		Rosenkranz and Poirier, 1979

peritoneal cavity and plated to determine the number of mutants (Salmonella) or recombinants (Saccharomyces) and the number of recovered microorganisms. Simultaneous experiments were conducted with control (untreated) mice. Using 25 mg/kg given intramuscularly, beryllium sulfate was not mutagenic with tester strain TA1530 or TA1538. Using 1200 mg/kg given orally, beryllium sulfate was not mutagenic in TA1535 and did not significantly increase the recombination frequency in *S. cerevisiae* D3.

6.1.3 Escherichia coli WP2 Assay

Negative mutagenic response in the *Escherichia coli* WP2 system was obtained with beryllium concentrations ranging from 0.1-10 µmol/plate (10.5 - 105 µg/plate) (Ishizawa, 1979).

These results should not be taken as proof, however, that beryllium is nonmutagenic. The standard test system may be insensitive for the detection of metal mutagens because of the large amount of magnesium salts, citrate, and phosphate in the minimal medium (McCann et al., 1975). Bacteria appear to be selective in letting metal ions get inside their cells. More research is needed to select a suitable strain of bacteria to detect metal-induced mutagenesis in these prokaryotic systems.

6.2 GENE MUTATIONS IN CULTURED MAMMALIAN CELLS

The ability of various beryllium compounds to cause gene mutations in cultured mammalian cells has been investigated by Miyaki et al. (1975) and Hsie et al. (1979a,b) (Table 6-2).

Miyaki et al. (1975) demonstrated the induction of 8-azaguanine-resistant mutants by beryllium chloride in the Chinese hamster V79 cells. Beryllium chloride at concentrations of 2 and 3 mM (158 µg/ml and 237 µg/ml, respectively) induced 35.01 ± 1.4 and 36.5 ± 1.7 mutant colonies per 10^6 survivors. These values were approximately 6 times higher than the control value of 5.8 ± 0.8 colonies per 10^6 survivors. The cell survival rates were 56.9 percent at 2 mM concentration and 39.4 percent at 3 mM. Analysis of mutant colonies revealed that they were deficient in the enzyme hypoxanthine guanine phosphoribosyl transferase (HGPRT) activity indicating that the mutation had occurred at the HGPRT locus.

Hsie et al. (1979a,b) also reported that beryllium sulfate induced 8-azaguanine-resistant mutants in Chinese hamster ovary (CHO) cells. However,

TABLE 6-2. MUTAGENICITY TESTING OF BERYLLIUM: GENE MUTATIONS IN MAMMALIAN CELLS *IN VITRO*

Test System	Strain	Concentration of Test Compounds	S-9 Activation System	Results	Comments	Reference
Chinese hamster	V79 cells; resistance to 8-azaguanine	2 mM (10 μg/ml) 3 mM (15 μg/ml) beryllium chloride	None	Reported positive 6.0 to 6.3-fold increase	1. 99 percent pure. 2. No dose response.	Miyaki et al., 1975
Chinese hamster	CHO cells; resistance to 8-azaguanine	Not stated	±	Reported mutagenic and weakly mutagenic	1. No details. 2. The authors noted variable results with noncarcinogens such as calcium.	Hsie et al., 1979 a,b

they did not provide details about the concentrations of the test compound and the number of mutants induced per 10^6 survivors.

These studies indicate that beryllium has the ability to cause gene mutations in cultured mammalian cells.

6.3 CHROMOSOMAL ABERRATIONS

Beryllium sulfate was tested for its clastogenic potential in cultured human lymphocytes and Syrian hamster embryo cells (Larramendy et al., 1981) (Table 6-3). Cultured human lymphocytes (24 hours old) were exposed to a single concentration, 2.82×10^{-5}M (5 µg/ml), of beryllium sulfate, and chromosome preparations were made 48 hr after the treatment. A minimum of 200 metaphases were scored for chromosomal aberrations. In cultures treated with beryllium, there were 19 cells (9.5 percent) with chromosomal aberrations, or 0.10 ± 0.02 aberration per metaphase. In the nontreated control cells, only 3 cells (1.5 percent) had chromosomal aberrations. This sixfold increase in the aberration frequency clearly indicates that beryllium sulfate is clastogenic in cultured human lymphocytes. A beryllium concentration of 2.82×10^{-5}M was selected because it induced a maximum number of sister chromatid exchanges in human lymphocytes in another experiment reported by the same authors (see Section 6.4).

In the Syrian hamster embryo cells the results were even more dramatic. This same concentration of beryllium sulfate 24 hr after the treatment induced aberrations in 38 out of 200 cells (19 percent). Aberration per metaphase was 0.12 ± 0.03. In control cells only 3 cells (1.5 percent) had aberrations or 0.01 ± 0.01 aberration per cell. In these studies, chromosomal gaps were also considered as aberrations. Even if the gaps were not included as true aberrations, the aberration frequency was still far above the control level, indicating that beryllium sulfate has a clastogenic potential in cultured mammalian cells.

6.4 SISTER CHROMATID EXCHANGES

Larramendy et al. (1981) also studied the potential of beryllium to induce sister chromatid exchanges (Table 6-3). Both cultured human lymphocytes and Syrian hamster embryo cells were employed in these studies.

Lymphocytes after 24 hr of cultivation were exposed to 5.6×10^{-6}M (1.0 µg/ml), 1.41×10^{-5}M (2.5 µg/ml) and 2.82×10^{-5}M (5 µg/ml) of beryllium sulfate

TABLE 6-3. MUTAGENICITY TESTING OF BERYLLIUM: MAMMALIAN IN VITRO CYTOGENETICS TESTS

Test System	Strain	Concentration of Test Compounds	S-9 Activation System	Results	Comments	Reference
Chromosomal aberrations	Human lymphocytes	2.82×10^{-5}M (5 μg/ml)	--	Reported positive	1. 6x above background level. 2. Primarily breaks.	Larramendy et al., 1981
Chromosomal aberrations	Syrian hamster embryo cells	2.82×10^{-5}M (5 μg/ml)	--	Reported positive	1. 12x above background level. 2. Primarily breaks and gaps.	Larramendy et al., 1981
Sister chromatid exchanges	Human lymphocytes	5.6×10^{-6}M (1 μg/ml) 1.41×10^{-5}M (2.5 μg/ml) 2.82×10^{-5} (5 μg/ml)	--	Reported positive	1. Less than two-fold increase. 2. Insufficient evidence for a positive conclusion.	Larramendy et al., 1981
Sister chromatid exchanges	Syrian hamster embryo cells	5.6×10^{-6}M (1 μg/ml) 1.41×10^{-5}M (2.5 μg/ml) 2.82×10^{-5}M (5 μg/ml)		Reported positive	1. Less than two-fold increase. 2. Insufficient evidence for a positive conclusion.	Larramendy et al., 1981

followed by 10 µg BrdUrd/ml medium. Cultures were incubated for an additional 48 hr and chromosome preparations were made and stained for sister chromatid exchange analysis. At least 30 metaphases were scored for each concentration of the test compound. The background sister chromatid exchange level was 11.30 ± 0.60. According to these investigators, there was a dose-dependent increase in sister chromatid exchanges, i.e., 17.75 ± 1.10, 18.15 ± 1.79, and 20.70 ± 1.01, respectively, for the above concentrations.

In the Syrian hamster embryo cells, the same concentrations of beryllium sulfate induced 16.75 ± 1.52, 18.40 ± 1.49, and 20.50 ± 0.98 sister chromatid exchanges. The background sister chromatid exchange frequency was 11.55 ± 0.84. The sister chromatid exchange assay has been extensively used in mutagenicity testing because of its sensitivity to many mutagenic chemicals.

The authors stated that the results of the sister chromatid exchange studies in human lymphocytes and Syrian hamster embryo cells demonstrated a dose-response relationship. However, in these studies, the increase was less than twofold and fell within a plateau region; thus, the dose-response relationship suggested by the authors may be somewhat tenuous. Further experimentation to confirm the study results would be advisable.

6.5 OTHER TESTS OF GENOTOXIC POTENTIAL

6.5.1 *The Rec Assay*

Kanematsu et al. (1980) found beryllium sulfate to be weakly mutagenic in the *Rec* assay. *Bacillus subtilis* strains H17 (*rec*$^+$) and M75 (*rec*$^-$) were streaked onto agar plates. An aqueous solution (0.05 ml) of 0.01 M (88.5 µg/plate) beryllium sulfate was added to a filter paper disk (10-mm diameter) which was placed on the plates at the starting point of the streak. Plates were first cold incubated (4°C) for 24 hr and then incubated at 37°C overnight. Inhibition of growth, due to DNA damage, was measured in both the wild type H17 (*rec*$^+$) and the sensitive type (*rec*$^-$) strains. The difference in growth inhibition between the wild-type strain and the sensitive strain was 4 mm, which was considered to indicate a weak mutagenic response. Similar results were also obtained by Kada et al. (1980).

6.5.2 *Pol Assay*

Beryllium was tested for mutagenicity in the *pol* assay using *Escherichia coli* (Rosenkranz and Poirier, 1979, 1980). Use for this assay is based on the fact that cells deficient in their ability to repair DNA damage are more sensitive than normal cells to the growth-inhibiting properties of mutagenic agents. Escherichia coli strains pol A^+ (normal) and pol A^- (DNA polymerase I-deficient) were grown on agar plates, and filter disks impregnated with 250 μg of beryllium sulfate were placed in the middle of each agar plate and incubated at 37°C for 7-12 hrs. Experiments were conducted both in the presence and absence of S-9 activation system. The diameter of the zones of growth were determined in both strains. There was no difference in the diameter of the zones of growth in both strains. Positive and negative controls were used for comparison. The shortcomings of this assay are that (1) interpretable conclusions can be drawn only when measurable zones of growth inhibition occur; (2) it is possible that the test chemical may not be able to penetrate the test organisms; and (3) insufficient diffusion of chemicals from the disk can occur because of low solubility or large molecular size.

6.5.3 Hepatocyte Primary Culture/DNA Repair Test

The DNA damage and repair test as reflected in unscheduled DNA synthesis (incorporation of tritiated thymidine) was conducted using beryllium sulfate (Williams et al., 1981). Rat primary hepatocyte cultures were exposed to 0.1, 1, and 10 mg/ml of beryllium sulfate with 10 μc/ml of tritiated thymidine and incubated for 18-20 hr. Following incubation, autoradiographs of cells were prepared. A minimum of 20 nuclei was counted for each concentration and the uptake of radioactive label was measured as grain counts in each nucleus. The compound was considered positive when the nuclear grain count was greater than that of the control (above 5 grains per nucleus over the control value). The compound was considered negative in the assay if the nuclear grain count was less than 5 at the highest nontoxic dose. Cytotoxicity was determined by the morphology of the cells. According to these authors, beryllium sulfate did not induce statistically greater grain count at any of the above concentrations over the control value. Benzo(a)pyrene was employed as a positive compound.

6.5.4 Beryllium-Induced DNA Cell Binding

Kubinski et al. (1981) reported that beryllium induces DNA protein complexes (adducts) that can be measured with analytical techniques. Escherichia coli cells and Ehrlick ascitis cells were treated with radioactive DNA in the presence of 30 μM of beryllium. Methyl methanesulfonate (MMS) was used as a positive control. The negative control consisted of cells only and radioactive DNA. The radioactive DNA bound to cell membrane proteins was measured. Like MMS, beryllium induced positive results. However, the significance of beryllium-induced DNA binding to cell membranes is not clear in terms of its ability to induce mutations.

6.5.5 Mitotic Recombination In Yeast

Beryllium sulfate did not induce mitotic recombination in the yeast *Saccharomyces cerevisiae* D_3 (Simmon, 1979b). The *Saccharomyces cerevisiae* strain D_3 is a heterozygote with mutations in ade 2 and his 8 of chromosome XV. When grown on a medium containing adenine, cells homozygous for the ade 2 mutation produce a red pigment. These homozygous mutants can be generated from the heterozygotes by mitotic recombination induced by mutagenic compounds. A single concentration (0.5 percent) of beryllium induced 10 mutant colonies per 10^5 survivors, while in the control the mutation frequency was 6 colonies per 10^5. In the mitotic recombination assay, there must be a 3-fold increase in the mutation frequency of experimental over the control in order to be considered as a positive mutagenic response. The negative mutagenic response of beryllium may be due to the fact that it is not able to penetrate into the cell as in other microbial tests.

6.5.6 Biochemical Evidence of Genotoxicity

In vitro exposure of rat liver cells to beryllium resulted in binding of beryllium to non-histone proteins that were phosphorylated (Parker and Stevens, 1979). Exposure of rat hepatosoma cells in tissue culture to beryllium reduced glucocorticoid induction of tyrosine transaminase activity (Perry et al., 1982). In a DNA fidelity assay, beryllium increased the misincorporation of nucleotide bases in the daughter strand of DNA that was synthesized *in vitro* from polynucleotide templates by microbial DNA polymerase (Zakour et al., 1981). Beryllium was investigated for its effects on the transcription of calf thymus DNA and phage T_4 DNA by RNA polymerase from *E. coli* under controlled conditions. Beryllium inhibited overall transcription but increased RNA chain irritation, indicating the interaction of the metal with the DNA template (Niyogi et al., 1981).

6.5.7 Mutagenicity Studies in Whole Animals

Information on the mutagenicity of beryllium compounds in intact animals such as *Drosophila* and mammals is not available in the literature. Such studies are highly valuable in assessing the in vivo effects of beryllium compounds, specifically to understand whether or not they induce mutations in germ cells. Metals such as cadmium and methyl mercury have been implicated in the induction of aneuploidy (numerical chromosomal aberrations) in female rodent germ cells. Aneuploidy is generally induced as a result of malfunctioning of the spindle apparatus. Such studies with beryllium compounds would yield valuable results.

7. CARCINOGENIC EFFECTS OF BERYLLIUM

The purpose of this section is to provide an evaluation of the likelihood that beryllium is a human carcinogen and, on the assumption that it is a human carcinogen, to provide a basis for estimating its public health impact, including a potency evaluation in relation to other carcinogens. The evaluation of carcinogenicity depends heavily on animal bioassays and epidemiologic evidence. However, information on mutagenicity and mechanisms of action, particularly in relation to interaction with DNA and to metabolic and pharmacokinetic behavior, has an important bearing on both the qualitative and quantitative assessment of carcinogenicity. The available information on these subjects is reviewed in other sections of this document. This section presents an evaluation of animal bioassays, human epidemiologic evidence, the dose-response (quantitative) aspects of assessment, and finally, a summary and conclusions dealing with all of the relevant aspects of the carcinogenicity of beryllium.

7.1 ANIMAL STUDIES

Numerous animal studies have been performed to determine whether or not beryllium and beryllium-containing substances are carcinogenic. In these studies, metallic beryllium, salts of beryllium, and beryllium-containing alloys and ores were administered by various routes. In the discussions that follow, the studies are grouped according to the routes of administration used.

7.1.1 Inhalation Studies

The first finding of pulmonary tumors after inhalation exposure to beryllium was reported by Vorwald in 1953. Among 15 female rats exposed to beryllium sulfate ($BeSO_4$) aerosol at a reported concentration of 33 μg beryllium/m^3, 7 hours/day, 5.5 days/week, 4 developed primary pulmonary adenocarcinomas. The incidence represented 80 percent (4/5) of animals necropsied after 420 days of exposure and 50 percent (4/8) of animals necropsied after one year or more. The paper reporting this study was read before a meeting of the American Cancer Society, but was never published; an abstract of the presentation was printed 2 years later (Vorwald et al., 1955). Schepers et al. (1957) published a paper updating the Vorwald et al. study, which then encompassed 136 rats, of which 78 survived to planned necropsy. The total number of tumors produced was counted, rather than the number of tumor-bearing animals. These tumors totaled 76 after the animals had had 6 months of exposure to the beryllium sulfate aerosol and up to 18 months of continued life in normal air. Eight histologic variants of neoplasms were observed, intrathoracic metastases were noted to occur, and successful transplants were claimed to have been accomplished.

During the late 1950s and early 1960s, both Schepers and Vorwald continued these experiments on what appears to have been a fairly large scale, but instead of writing papers on them in the customary way, the results were hinted at, or partially incorporated into reviews (Schepers, 1961; Vorwald et al., 1966). The details of these experiments are, therefore, not in the public record. Based on all available information, the best estimates are that Schepers exposed rats to beryllium phosphate and obtained a tumor incidence of 35-60/170 at 32-35 μg beryllium/m^3 and 7/40 at 227 μg beryllium/m^3 (20-35 percent and 17.5 percent, respectively); after exposure to beryllium fluoride he obtained a tumor incidence of 10-20/200 at 9 μg beryllium/m^3 (5-10 percent), and after exposure to zinc beryllium manganese silicate ($ZnBeMnSiO_3$) (a fluorescent phosphor in use at that time) he obtained a tumor incidence of 4-20/220 at 0.85-1.25 mg beryllium/m^3 (2-9 percent, Table 7-1). No tumors were observed in rabbits and guinea pigs similarly exposed.

In all but one of his inhalation experiments, Vorwald used rats exposed to beryllium sulfate aerosol in concentrations ranging from 2.8 to 180 μg beryllium/m^3 on various exposure schedules ranging in length from 3 months to 24 months. In one inhalation experiment, beryllium oxide (temperature of firing not known) was used at 9 mg/m^3. Pulmonary lesions believed to be adenocarcinomas were found in all groups, in incidences ranging from 20 to 100 percent, with weak correlations between incidence and exposure concentration and between incidence and exposure length (Table 7-2). No metastases were observed. Serial homotransplants were attempted and were unsuccessful.

Reeves et al. (1967) exposed 150 rats of both sexes, and an equal number of controls, to beryllium sulfate aerosol at a mean atmospheric concentration (±1 S.D.) of 34.25 ± 23.66 μg beryllium/m^3 on a schedule of 35 hours/week. Scheduled sacrifices were conducted quarterly. The first lung tumors were seen at 9 months' exposure, and all animals necropsied at 13 months (43/43) had pulmonary adenocarcinomas. Essentially similar results were reported by Reeves and Deitch (1969) 2 years later for another animal group. In the latter study, 225 female rats were exposed for durations of 3 to 18 months to

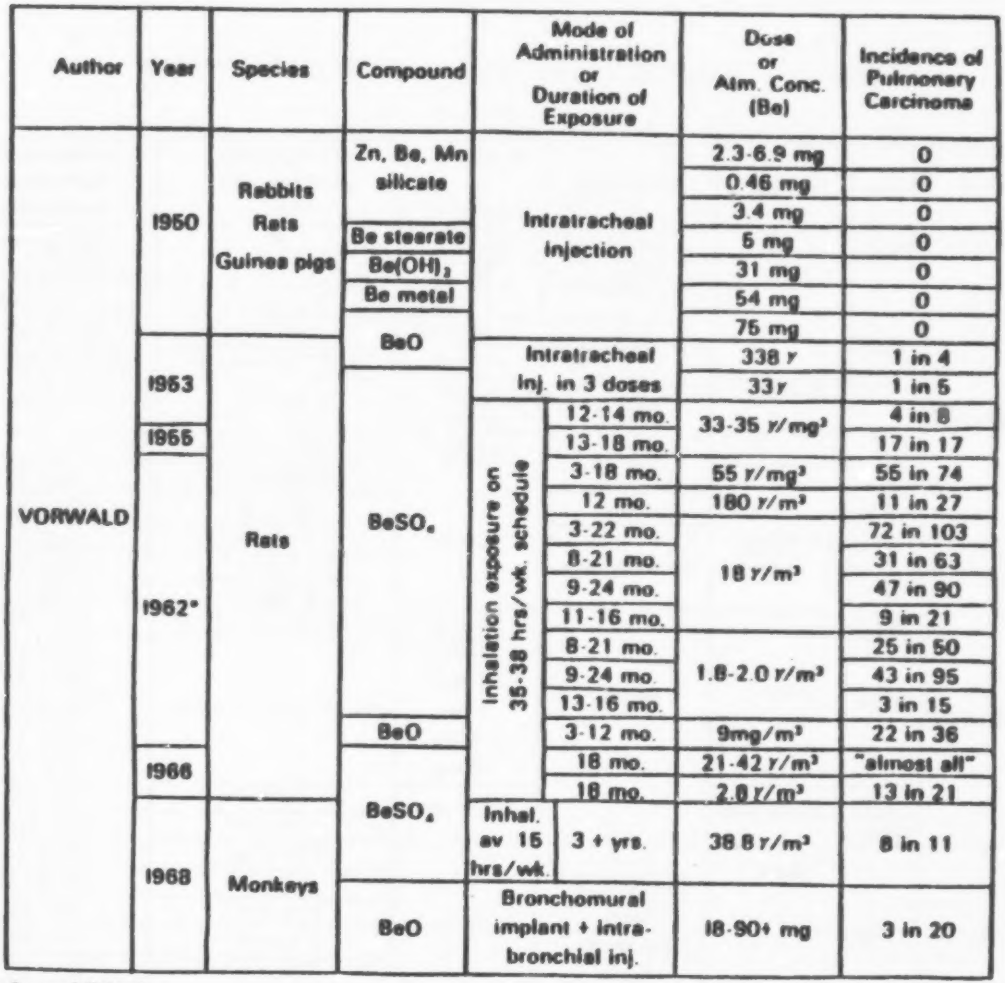
TABLE 7-1. PULMONARY CARCINOMA FROM BERYLLIUM PART 2

Author	Year	Species	Compound	Duration of Exposure	Atmospheric Concentration Be	Incidence of Pulmonary Carcinoma
SCHEPERS	1957	Rats	$BeSO_4$	6-9 mo.	32-35 γ/m^3	58? in 136
	1961		Be phosphate	1-12 mo.		ca. 35-60 in 170
					227 γ/m^3	ca. 7 in 40
			BeF_2	6-15 mo.	9 γ/m^3	ca. 10-12 in 200
			Zn, Be, Mn silicate	1-9 mo.	0.85-1.25 mg/m^3	ca. 4-20 in 220
		Rabbits		24 mo.	1 mg/m^3	0
		Guinea pigs		22 mo.		0
			$BeSO_4$	12 mo.	35 γ/m^3	0
	1964	Monkeys		8 mo.	35-200 γ/m^3	0 in 4
			BeF_2		180 γ/m^3	0 in 4
			Be phosphate		0.2 mg/m^3	0 in 4
					1.1 mg/m^3	1 in 4
					8.3 mg/m^3	0 in 4
REEVES	1967	Rats	$BeSO_4$	13 mo.	34.25 ± 23.66 γ/m^3	43 in 43
	1969			3 mo.	35.66 ± 13.77 γ/m^3	19 in 22
				6 mo.		33 in 33
				9 mo.		15 in 15
				12 mo.		21 in 21
				18 mo.		13 in 15
	1972	Guinea pigs		18-24 mo.	3.7-30.4 γ/m^3	0 in 58
	1976*				~ 15 γ/m^3	0 in 110
WAGNER	1969	Rats	Beryl	17+ mo.	620 γ/m^3	18 in 19
			Bertrandite		210 γ/m^3	0 in 30-60
		Hamsters	Beryl		620 γ/m^3	0 in 48
			Bertrandite		210 γ/m^3	0 in 48
		Monkeys	Beryl		620 γ/m^3	0 in 12
			Bertrandite		210 γ/m^3	0 in 12

*unpublished

Source: Reeves (1978)

TABLE 7-2. PULMONARY CARCINOMA FROM BERYLLIUM PART 1



Author	Year	Species	Compound	Mode of Administration or Duration of Exposure		Dose or Atm. Conc. (Be)	Incidence of Pulmonary Carcinoma
VORWALD	1950	Rabbits Rats Guinea pigs	Zn, Be, Mn silicate	Intratracheal injection		2.3-6.9 mg	0
						0.46 mg	0
						3.4 mg	0
			Be stearate			5 mg	0
			$Be(OH)_2$			31 mg	0
			Be metal			54 mg	0
			BeO			75 mg	0
	1953	Rats		Intratracheal inj. in 3 doses		338 γ	1 in 4
			$BeSO_4$			33 γ	1 in 5
				Inhalation exposure on 35-38 hrs/wk. schedule	12-14 mo.	33-35 γ/mg^3	4 in 8
	1955				13-18 mo.		17 in 17
	1962*				3-18 mo.	55 γ/mg^3	55 in 74
					12 mo.	180 γ/m^3	11 in 27
					3-22 mo.	18 γ/m^3	72 in 103
					8-21 mo.		31 in 63
					9-24 mo.		47 in 90
					11-16 mo.		9 in 21
					8-21 mo.	1.8-2.0 γ/m^3	25 in 50
					9-24 mo.		43 in 95
					13-16 mo.		3 in 15
			BeO		3-12 mo.	9mg/m^3	22 in 36
	1966		$BeSO_4$		18 mo.	21-42 γ/m^3	"almost all"
					18 mo.	2.8 γ/m^3	13 in 21
	1968	Monkeys		Inhal. av 15 hrs/wk.	3 + yrs.	38 8 γ/m^3	8 in 11
			BeO	Bronchomural implant + intrabronchial inj.		18-90+ mg	3 in 20

*unpublishod

Source: Reeves (1978)

35.66 ± 13.77 μg beryllium/m^3 (35 hours/week) at various age levels (Figure 7-1). It was found that tumor yield depended not on length of exposure but on how early in life the exposure was received. Rats exposed at an early age for only 3 months had essentially the same tumor frequency (19/22) as rats exposed for the full 18 months (13/15), whereas rats receiving 3 months' exposure later in life had substantially reduced tumor counts (3-10/20-25; 86-87 percent versus 15-40 percent). Generally, an incubation time of at least 9 months after commencement of exposure was required to produce actual tumors, whereas epithelial hyperplasia of the alveolar surfaces commenced after about 1 month, progressed to metaplasia by 5-6 months, and to anaplasia by 7-8 months. In guinea pigs, 18 months of exposure (35 hours/week) to three different concentrations of beryllium sulfate (3.7 ± 1.5 μg beryllium/m^3, 16.6 ± 8.7 μg beryllium/m^3, and 30.4 ± 10.7 μg beryllium/m^3) produced no tumors, but only alveolar hyperplasia/metaplasia in 23 out of 144 animals, all of them associated with diffuse interstitial pneumonitis. Incidence of hyperplasia/metaplasia in unexposed controls was 3/55 (Reeves et al., 1971, 1972; Reeves and Krivanek, 1974). Sanders et al. (1978) exposed female rats to submicron aerosols of medium-fired (1000°C) beryllium oxide by the nose-only method. Only 1 of 184 rats developed a lung tumor during the 2-year observation period; alveolar deposition was 1-91 μg beryllium with a half-time of 325 days.

Wagner et al. (1969) exposed rats, hamsters, and squirrel monkeys to aerosols of beryl ore and bertrandite ore at the then "nuisance limit" for all dusts (15 mg/m^3). At this particle concentration, the beryllium content of the aerosols was 620 and 210 μg/m^3 for beryl and bertrandite, respectively. Exposure was continued intermittently for 17 months. At that point, 18 of 19 rats exposed to beryl dust had bronchiolar or alveolar cell tumors, of which 7 were judged to be adenomas, 9 adenocarcinomas, and 2 epidermoid tumors. Metastases were not observed, and transplants were not attempted. In the animals exposed to bertrandite dust, and in all hamsters and squirrel monkeys, no indisputable tumors were found. In the bertrandite-exposed rats and hamsters, granulomatous lesions composed of large, tightly packed macrophages as well as "atypical proliferation" of the cells lining the respiratory bronchioles and alveoli were seen. Atypical proliferation was also seen in beryl-exposed hamsters, and, according to the authors, these proliferations "could be considered alveolar cell tumors except for their size." Only the granulomatous lesions were seen in both beryl- and bertrandite-exposed monkeys.

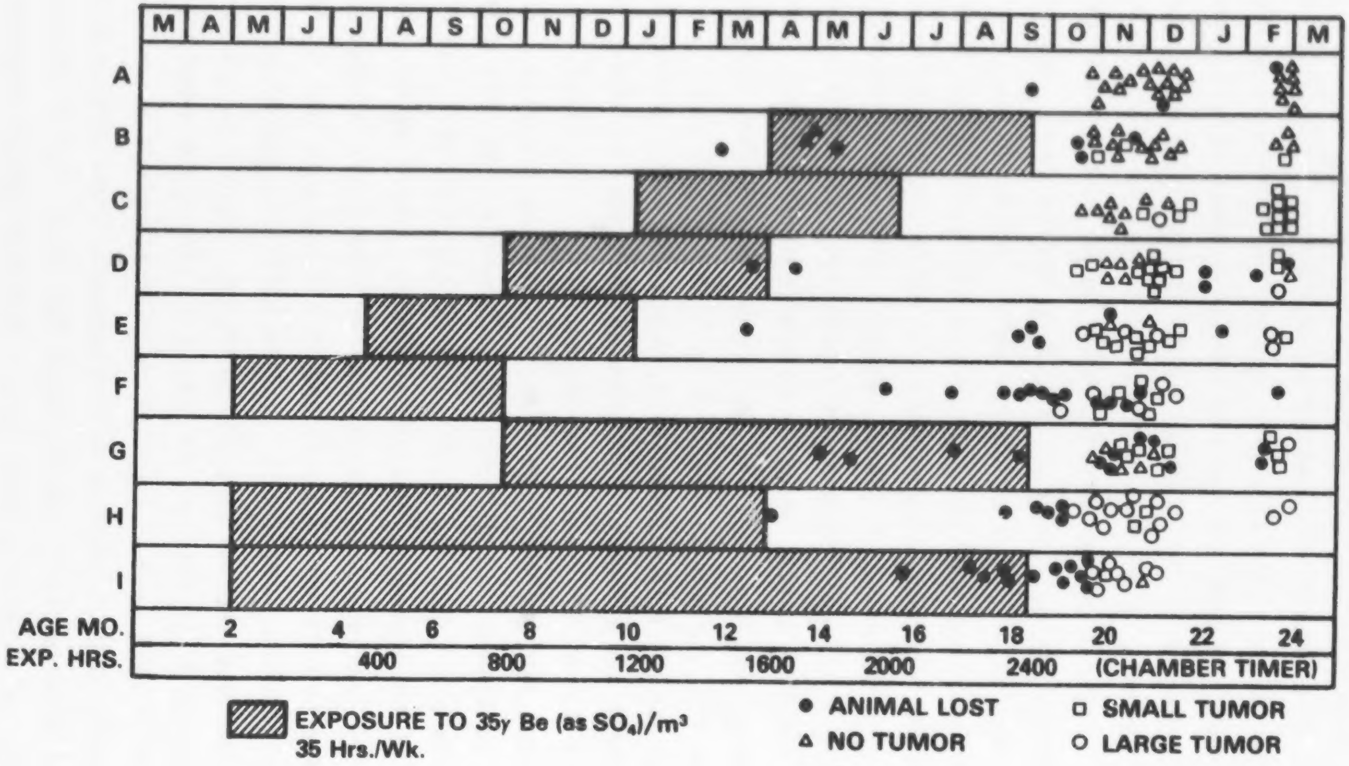


Figure 7-1. Pulmonary tumor incidence in female rats, 1965-1967.

Source: Reeves and Deitch (1969).

Schepers (1964) found that among 20 female rhesus monkeys exposed to inhalation of beryllium sulfate ($BeSO_4$), beryllium phosphate ($BeHPO_4$), or beryllium fluoride (BeF_2), in concentrations ranging from 0.035 to 8.3 mg beryllium/m^3, one animal had a small pulmonary neoplasm that appeared to be an alveolar carcinoma. The animal was in the beryllium phosphate (1.1 mg beryllium/m^3) exposure group, and the tumor, which had a maximum diameter of 3 mm, was found on the 82nd day following commencement of exposure. Its connection with the beryllium exposure was judged to be uncertain.

Vorwald (1968) reported the outcome of a 3-year chamber study on rhesus monkeys inhaling an aerosol of beryllium sulfate, with intermittent exposure averaging about 15 hours/week, at a mean atmospheric concentration of 38.8 µg beryllium/m^3. Eight of 11 surviving monkeys had pulmonary tumors, with adenomatous patterns predominating among areas with epidermoid characteristics. Extensive metastases to the mediastinal lymph nodes, and in some animals to the bones, liver, and adrenals, were seen. No control animals were kept in this experiment.

Dutra et al. (1951) exposed 5, 6, and 8 rabbits to beryllium oxide aerosol (degree of firing unidentified) at 1, 6, and 30 mg beryllium/m^3, respectively, on a 25-hours/week schedule for 9-13 months. One rabbit in the 6 mg beryllium/m^3 group developed osteosarcoma of the pubic bone, with extension into the contiguous musculature. Scattered tumors, which were judged to be metastases of the osteogenic sarcoma, were seen in the lungs and spleen. The lungs also exhibited extensive emphysema, interstitial fibrosis, and lymphocytic infiltration. Rabbits in the other groups remained free of malignancies.

7.1.2 Intratracheal Injection Studies

Intratracheal administration of beryllium compounds was practiced as a shortcut for inhalation experiments by Vorwald (1953), Van Cleave and Kaylor (1955), Spencer et al. (1965), Kuznetsov et al. (1974), Ishinishi et al. (1980), and Groth et al. (1980). The fate and effects of these deposits are not necessarily the same as that of identical compounds deposited by inhalation. The intratracheal injection produces an unnatural deposition pattern in the lung and also allows the pulmonary entry of larger particles, those that normally would be filtered out in the upper respiratory tract. Dusts of a certain compound, therefore, frequently show longer pulmonary half-times after intratracheal injection than after inhalation.

Vorwald (1953) reported one lung tumor after intratracheal injection of 338 μg beryllium (as beryllium oxide) and one "sarcoma" (site unidentified) after intratracheal injection of 33.8 μg beryllium (as beryllium sulfate); the induction of lung cancer with intrathoracic metastases in rhesus monkeys following intrabronchial injection and/or bronchomural implantation of "pure" beryllium oxide (firing temperature unknown) was also mentioned in a review, without reference to any original publication (Vorwald et al., 1966).

Groth et al. (1980) injected dusts of beryllium metal, passivated beryllium metal (with < 1 percent chromium) and various beryllium alloys, as well as beryllium hydroxide, intratracheally into rats. Lung tumors were observed after injection of beryllium metal, passivated beryllium metal, and a beryllium-aluminum alloy (containing 62 percent beryllium), but not after injection of other beryllium alloys in which the beryllium concentration was < 4 percent; injection of beryllium hydroxide into 25 rats yielded 13 cases of neoplasia, of which 6 were judged to be adenomas and 7 were adenocarcinomas (Table 7-3). The rest of the animals had various degrees of metaplasia, which was regarded as precancerous lesions. Several of the tumors were successfully transplanted.

The most detailed studies with intratracheal injections of beryllium were reported by Spencer et al. (1965, 1972). High-fired (1600°C), medium-fired (1100°C), and low-fired (500°C) specimens of beryllium oxide were injected into rats; the incidence of pulmonary adenocarcinomas was 3/28, 3/19, and 23/45 in the three groups, respectively, corresponding to 11, 16, and 51 percent.

Ishinishi et al. (1980) injected 30 rats with beryllium oxide (calcined at 900°C) by the intratracheal route, in 15 weekly doses of 1 mg each. Of 29 animals examined 1.5 years later, 7 (24 percent) had lung tumors, i.e., one squamous cell carcinoma, one adenocarcinoma, four adenomas, and one malignant lymphoma. Of the four adenomas, three had "strong histological architectures [of] suspected malignancy" (Tables 7-4 and 7-5). The malignant lymphoma was found not only in the lung but also in the hilar lymph nodes and in the abdominal cavity, with the primary site remaining undetermined. Six extrapulmonary lymphosarcomas, fibrosarcomas, or other tumors were found in further injected animals but in only one of 16 control animals. The incidence of clearly malignant primary pulmonary tumors in this experiment was 2/29, or 7 percent.

TABLE 7-3. BERYLLIUM ALLOYS--LUNG NEOPLASMS

Compounds	Dose of compound (mg)	Dose of Be (mg)	Total no. rats autopsied	Autopsy intervals and lung neoplasm incidences (months)					P value[a]
				1	2-7	8-10	11-13	16-19	
Be metal	2.5	2.5	16	0/5[b]	-	-	3/5	6/6	<0.0001
Be metal	0.5	0.5	21	0/5	0/3	0/5	0/5	2/3	0.011
Passivated Be metal	2.5	2.5	26	0/5	0/2	1/5	4/10	4/4	<0.0001
Passivated Be metal	0.5	0.5	20	0/5	0/1	0/3	-	7/11	0.0001
BeAl alloy	2.5	1.55	24	0/5	0/3	2/5	0/5	2/6	0.043
BeAl alloy	0.5	0.3	21	0/5	-	0/1	0/6	1/9	0.30
4% BeCu alloy	2.5	0.1	28	0/5	0/1	0/5	0/6	0/11	
4% BeCu alloy	0.5	0.02	24	0/5	0/2	-	0/4	0/13	
2.2% BeNi alloy	2.5	0.056	28	0/5	0/1	0/5	0/5	0/12	
2.2% BeNi alloy	0.5	0.011	27	0/5	0/2	-	0/5	0/15	
2.4% BeCuCo alloy	2.5	0.06	33	0/5	0/3	0/5	0/5	0/15	
2.4% BeCuCo alloy	0.5	0.012	30	0/5	0/2	-	0/5	0/18	
Saline	-	-	39	0/5	0/3	0/5	0/5	0/21	

[a] P value (Fisher's one-tailed test) when the lung neoplasm incidence in exposed groups is compared with the lung neoplasm incidence in the saline control group at the autopsy period of 16-19 months. Because of multiple comparisons with the control group, the individual P value must be 0.008 or less to be significant.

[b] Number of rats with a lung neoplasm divided by total number of rats autopsied at the specified interval.

Source: Groth et al. (1980)

TABLE 7-4. LUNG TUMOR INCIDENCE IN RATS AMONG BeO, As_2O_3 AND CONTROL GROUPS

Group	Sex	Number of rats surviving after 15 instillations	Average	Range	Malignant tumor	Benign tumor
BeO (1 mg)*	M	30/30	545	99-791	2+(1)[Δ]	4
As_2O_3 (1 mg)*	M	19/30	546	98-820	1	0
Control	M	16	398	1-617	0	0

*Amount of one instillation Be or As.

[Δ] Unknown which is primary tumor or metastasis.

Source: Ishinishi et al. (1980)

TABLE 7-5. HISTOLOGICAL CLASSIFICATION OF LUNG TUMORS AND OTHER PATHOLOGICAL CHANGES

			Malignant tumors (A)			Benign tumors (B)				
Group	Sex	No. of rats	Squamous cell carcinoma	Adeno-carcinoma	Malignant lymphoma	Ade-noma	All tumors (A + B) [tumor incidence rats]	Squamous cell meta-plasia	Osseous metaplasia	Other site tumors except the lung tumor
BeO (1 mg as Be)	M	29*	1[a]	1[b]	(1)[c]	4(3)[Δ]	21.4%	2	1	6[d]
As_2O_3 (a mg as As)	M	18*	1	0	0	0	5.6%	5	2	3[e]
Control	M	16	0	0	0	0	0	1	0	1

[a] Coexistence of squamous cell carcinoma and adenocarcinoma.

[b] Coexistence of adenocarcinoma and adenoma.

[c] Malignant lymphoma in the left lobule of the lung, the lymphatic nodules in the pulmonary hilus, and in the abdominal cavity.

[d] Lymphosarcoma or fibrosarcomas (except one).

[e] Mesothelioma in peritoneum, liver and mesentery.

*One rat was not histopathologically observed because of cannibalism.

[Δ] Three of four adenomas have strong histological architectures of suspected malignancy.

Source: Ishinishi et al. (1980)

7.1.3 Intravenous Injection Studies

In 1946, Gardner and Heslington, in a search to find the cause of an "unusual incidence of pulmonary sarcoid" in the fluorescent light tube industry, injected zinc beryllium silicate ($ZnBeSiO_3$) into rabbits and obtained osteosarcoma of the long bones in all seven animals which survived the treatment for 7 months or more. Because this was the first instance of experimental carcinogenesis by an inorganic substance, it evoked great interest. Beryllium was clearly implicated as the causative agent because zinc oxide, zinc silicate, or silicic acid did not cause osteosarcoma in a second set of trials, whereas beryllium oxide (firing temperature unknown) did. Guinea pigs and rats, when similarly treated with both zinc beryllium silicate and beryllium oxide, failed to respond. The dose of beryllium within the two compounds injected (beryllium oxide and zinc beryllium silicate) was 360 and 60 mg, respectively, in 20 divided doses during a 6-week period.

This basic experiment was repeated many times by several investigators (Tables 7-6 and 7-7). Cloudman et al. (1949) produced osteosarcoma in four out of five rabbits receiving a total dose of 17 mg beryllium (as zinc beryllium silicate); mice were also injected, with production of "some" tumors (count or incidence percentages not stated). In this experiment, "substantially 100 percent beryllium oxide by spectrographic standards" (degree of firing not stated, total dose 1.54-390 mg beryllium) produced no tumors. Nash (1950) produced five cases of osteosarcoma with zinc beryllium silicate phosphor among 28 injected rabbits, with about 200 mg zinc beryllium silicate (12 mg beryllium) appearing to be the minimum effective dose. Dutra and Largent (1950) produced osteosarcoma in rabbits with both zinc beryllium silicate (2/3) and beryllium oxide (6/6), and reported a successful transplant in the anterior chamber of the eye of a guinea pig. Barnes et al. (1950) produced six cases of osteosarcoma among 17 rabbits injected with zinc beryllium silicate and one case of osteosarcoma among 11 rabbits injected with beryllium silicate. The tumors were multicentric in origin; blood-born metastases were stated to be common. Hoagland et al. (1950) injected rabbits with 2 samples of zinc beryllium silicate phosphor, containing 2.3 and 14 percent beryllium oxide, and produced an osteosarcoma incidence of 3/6 and 3/4, respectively. With uncompounded BeO, the incidence was 1/8; beryllium phosphate produced no tumors. The osteosarcomas appeared to be highly invasive, but could not be transplanted.

TABLE 7-6. OSTEOGENIC SARCOMAS IN RABBITS[a]

Compound	Dose of compound (g)	Dose of beryllium (mg)	Route of injection	No. of animals with tumors	Incidence of tumors	Incidence of metastases	Reference
$ZnBeSiO_3$	1	UN	iv	7	7/7 (100%)	3/7 (43%)	
BeO	1	360	iv	1	UN	UN	Gardner and Heslington, 1946
$ZnBeSiO_3$	UN	17	iv	4	4/5 (80%)	3/4 (75%)	
$ZnBeSiO_3$	UN	0.264	iv(M)	1	UN	UN	Cloudman et al., 1949
$ZnMnBeSiO_3$	0.45-0.85	3.7-7.0	iv	3	≥ 3/6 (50%)		
$ZnMnBeSiO_3$	0.2	10-12.6	iv	3	≥ 3/4 (75%)	5/7 (71%)	Hoagland et al., 1950
BeO	UN	360	iv	1	≥ 1/9 (11%)		
Be metal	0.04	40	iv	2	2/5 (40%)	UN	Barnes et al., 1950
$ZnBeSiO_3$	1-2.1	7.2-15	iv	6	6/13 (46%)	4/6 (67%)	
$BeSiO_3$	1-1.2	UN	iv	1	1/8 (13%)	None	Barnes et al., 1950
$ZnBeSiO_3$	UN	64-90	iv	2	2/3 (67%)	2/2 (100%)	
BeO	UN	360-700	iv	6	6/6 (100%)	6/6 (100%)	Dutra and Largent, 1950
$ZnBeSiO_3$	1	12	iv	5	5/10 (50%)	>2/5 (40%)	Janes et al., 1954
$ZnBeSiO_3$	1	12	iv	10	10/13 (77%)	UN	Kelly et al., 1961
BeO	1	360	iv	3	UN	2/3 (66%)	Komitowski, 1967
Be phosphate	0.103	UN	iv	1	UN	UN	Vorwald, 1950
BeO	0.22-0.4	79-144	IMD	7	7/9 (78%)	UN	
BeO	0.42-0.6	151-216	IMD	11	11/11 (100%)	UN	Yamaguchi, 1963
$ZnBeSiO_3$	0.02	0.144	IMD	4	4/12 (33%)	3/4 (75%)	Tapp, 1969
BeO	Inhalation 6 mg Be/M^3			1	≥ 1/6 (≥17%)	1/1 (100%)	Dutra et al., 1951
Totals for $ZnBeSiO_3$ + $ZnMnBeSiO_3$			iv	40	40/61 (66%)	≥ 18/30 (60%)	

[a] UN = unknown; IMD = intramedullary; $ZnBeSiO_3$ = zinc beryllium silicate; (M) = mouse; $ZnMnBeSiO_3$ = zinc manganese beryllium silicate; BeO = beryllium oxide.

Source: Groth (1980)

TABLE 7-7. OSTEOSARCOMA FROM BERYLLIUM

Author	Year	Species	Compound	Mode of Administration	Total Dose (mg Be)	Incidence of Osteosarcoma
GARDNER	1946	Rabbits	Zn Be silicate	I.v. in 20 doses	60	7 in 7
			BeO		360	1 in ?
		Guinea pigs	Zn Be silicate		60	0
			BeO		360	0
		Rats	Zn Be silicate		60	0
			BeO		360	0
CLOUDMAN	1949	Rabbits	Zn Be silicate	I.v. in 20-22 doses	17	4 in 5
			BeO		140	0
		Mice	Zn Be silicate		0.26	"some"
			BeO		0.55	0
BARNES	1950	Rabbits	Zn Be silicate	I.v. in 6-10 doses	7.2	4 in 14
					16	2 in 3
			BeO		180	1 in 11
HOAGLAND	1950	Rabbits	Zn Be silicate (BeO = 2.3%)	I.v. in 1-30 doses	3-7	3 in 6
			Zn Be silicate (BeO = 14%)		10-12	3 in 4
			Be phosphate		130?	0 in 5
			BeO		360	1 in 8
NASH	1950	Rabbits	Zn Be silicate	I.v. "repeated"	12+	5 in 28
DUTRA	1950	Rabbits		I.v. in 17-25 doses	64-90	2 in 3
			BeO	I.v. in 20-26 doses	360-700	6 in 6
	1951			Inhalation 25 hrs/wk 9-10 months	1*	0 in 5
					6*	1 in 6
					30*	0 in 8
JANES	1954	Rabbits	Zn Be silicate	I.v. in 20 doses	12	5 in 10
	1956	Splenectomized rabbits			12	7 in 7
KELLY	1961	Rabbits			12	10 in 14
HIGGINS	1964	Rabbits			3300	"many"

*atmospheric concentration in mg Be/m^3

Source: Reeves (1978)

Araki et al. (1964) injected 35 rabbits with zinc beryllium manganese silicate ($ZnBeMnSio_3$), zinc beryllium silicate ($ZnBeSiO_3$), or beryllium phosphate ($BeHPO_4$). The incidence of osteosarcoma was 6/24, 2/7, and 2/4 in the three groups, respectively; there were no tumors among three rabbits injected with beryllium oxide (firing temperature unstated) or among two uninjected controls. There was also a primary thyroid tumor in the group injected with zinc beryllium manganese silicate. Liver cirrhosis and splenic fibrosis were also observed; transplant experiments were all negative.

Several experiments were reported from the Mayo Foundation (Janes et al., 1954, 1956; Kelly et al., 1961) which also confirmed the carcinogenic effects of intravenous beryllium on bone. Out of a combined total of 31 rabbits receiving zinc beryllium silicate in a total dose of 12 mg beryllium, 22 developed osteosarcomas. New bone formation was observed in the medullary cavities of the long bones before the malignant changes became apparent. Of particular interest were observations of atrophy of the spleen in those animals in which bone tumors developed, while in the injected rabbits that did not develop the bone tumors, the spleen seemed to be normal. Following splenectomy, the incidence of bone tumor or new bone formation in the medullary cavity was 100 percent, whereas the incidence of these developments in non-splenectomized rabbits after identical injection was only 50 percent. The results suggest that a well-functioning spleen may serve as protection against beryllium carcinogenesis in the rabbit. Tibial chondrosarcomas were also produced, and successful transplants to the anterior chambers of the eyes of rabbits were performed (Higgins et al., 1964).

7.1.4 Intramedullary Injection Studies

Beryllium oxide or zinc beryllium silicate was directly introduced into the medullary cavity of bones of rabbits by Yamaguchi (1963), Tapp (1969), and Fodor (1977). Osteosarcoma, chondrosarcoma, and presarcomatous changes (irregular bone formation) were observed; 20-30 injections (20 mg beryllium oxide per injection) gave the highest frequency of tumor formation. The tumors developed directly from the medullary bone, and were sometimes preceded by fibrosis. They metastasized to liver, kidney, lymph nodes, and in especially high frequency, to the lung.

7.1.5 Intracutaneous Injection Studies

No neoplasms were produced by intracutaneous injection of beryllium sulfate, or by introduction of insoluble beryllium compounds (beryllium oxide, beryllium phosphate, beryllium-containing fluorescent phosphors) into accidental cuts of the skin. The lesions thus produced were cutaneous granulomas, or, in the case of extensive injury, necrotizing granulomatous ulcerations (Van Ordstrand et al., 1945; Reeves and Krivanek, 1974).

Intracutaneous administration of beryllium sulfate in doses of 5 μg beryllium was practiced in the immunotoxicologic experiments of Reeves et al. (1971, 1972); there was no evidence that measurable amounts of beryllium left the sites of administration.

7.1.6 The Percutaneous Route of Exposure

No neoplasms were ever observed following the percutaneous route of exposure in any species. Eczematous contact dermatitis in humans following work with soluble compounds of beryllium was first described by Van Ordstrand et al. (1945), and Curtis (1951) studied the allergic etiology of these reactions and developed a patch test. In 1955, Sneddon reported that a patient with a patch test positive to beryllium developed a sarcoid-like granuloma at the test site. Granulomatous ulcerations followed if insoluble beryllium compounds became imbedded in the skin. Dutra et al. (1951) could produce experimental beryllium granulomas in the skin of pigs which resembled the human lesion. There is no record of any of these lesions ever undergoing malignant degeneration.

In view of the virtual impenetrability of the intact skin to beryllium (section 4.1.3), the fact that no neoplasms were observed to occur by the percutaneous route of exposure could be explained by the lack of absorption through intact skin.

7.1.7 Dietary Route of Exposure

No neoplasms have ever been known to be observed following beryllium exposure by the dietary route in any species. Guyatt et al. (1933), Jacobson (1933), and Kay and Skill (1934) produced rickets in young rats fed beryllium carbonate at 0.1-0.5 percent dietary level. This result is attributable to intestinal precipitation of beryllium phosphate and consequent phosphorus deprivation. Sols and Dierssen (1951) observed a decrease in the intestinal absorption of glucose at similar intake concentrations, attributable to inhibition of alkaline phosphatase (Du Bois et al., 1949). At intake levels of 5-500 ppm in diet, no toxic effects of any kind were found (Reeves, 1965; Schroeder and Mitchener, 1975; Morgareidge et al., 1977).

If insoluble beryllium dusts (beryllium, beryllium alloys, beryllium oxide, beryllium phosphate, beryllium ores) are ingested, the bulk of these substances will pass through the gastrointestinal tract unabsorbed. Depending on the size of the particles, and, in the case of beryllium oxide, on the firing temperature, a minor proportion of these dusts could become dissolved in gastric juices, and traces of the resultant beryllium chloride could be absorbed from the stomach. Upon entry into the intestine, any dissolved beryllium would become precipitated again, mainly as beryllium phosphate (Reeves, 1965).

Soluble beryllium salts [beryllium fluoride (BeF_2), beryllium chloride ($BeCl_2$), beryllium sulfate ($BeSO_4$), and beryllium nitrate ($Be[NO_3]_2$)] are available for absorption in the stomach, to the extent that there is alimentary absorption from the stomach, which in most mammalian species is recognized as very minor. At levels of intake of 0.6-6.6 μg beryllium/day in the drinking water of rats, 80+ percent of the intake passed the gastrointestinal tract unabsorbed. Upon entering the alkaline milieu of the intestine, the beryllium became precipitated and was excreted in the feces (Reeves, 1965; Furchner et al., 1972; Schroeder and Mitchener, 1975). There is some evidence that increasing the intake concentration does not increase the amount absorbed from the intestine, because the latter is governed by the solubility of the intestinal precipitates rather than by the total beryllium levels present.

7.1.8 Tumor Type, Species Specificity, Carcinogenic Forms, and Dose-Response

7.1.8.1 Tumor Type and Proofs of Malignancy--The pulmonary neoplasms found in rats after beryllium exposure were classified as adenocarcinomas, showing a predominantly alveolar pattern. Reeves et al. (1967) distinguished four histological variants, including focal columnar, focal squamous, focal vacuolar, and focal mucigenous. Schepers et al. (1957) distinguished several more, including some adenomas not judged to be malignant. Wagner et al. (1969) and Groth et al. (1980) found that about half of the tumors they produced with beryllium were benign adenomas. The diagnosis of pathological lesions is complicated, and requires judgment and special experience. The histological differentiation between adenomas and adenocarcinomas is not always well defined, and may also have species-related peculiarities, so that different conclusions on the same specimen may sometimes be reached by pathologists, and especially by those who have been trained in human medicine rather than veterinary medicine. It is also noteworthy that neoplasia in the lungs of rats was invariably associated with the purulent lesions of chronic murine pneumonia, which itself was exacerbated by inhalation of the acidic beryllium sulfate aerosol.

Metastases as well as successful transplants were claimed by Schepers et al. (1957); neither were explicitly observed or successfully accomplished in the rat experiments of Vorwald, although this was reported with ambiguity when these studies were published (Vorwald et al., 1966; see also Lesser, 1977). In the monkey experiments of Vorwald (1968), which lacked controls, extensive metastases to the mediastinal lymph nodes and sometimes to the bones, liver, and adrenals were reported. Groth et al. (1980) accomplished successful transplants in experiments with intratracheal administration of beryllium metal and beryllium alloy, but metastasis to the mediastinal lymph node was observed in only one animal.

The bone neoplasms produced with intravenous or intramedullary administration of beryllium to rabbits are surrounded with considerably less uncertainty. The malignant osteosarcoma or chondrosarcoma character of these neoplasms has not been challenged, and metastases to all parts of the body were observed--but it is noteworthy that the transplant experience in these studies was nonuniform. Successful transplants to the anterior chamber of the eye were reported by Dutra and Largent (1950) and Higgins et al. (1964), whereas failure with transplants was expressly admitted by Hoagland et al. (1950) and Araki et al. (1954). It is possible that the degree of malignancy of the bone tumors depended somewhat on the type of compound used in the injection.

7.1.8.2 Species Specificity and Immunobiology--Pulmonary tumors were produced after inhalation exposure and sometimes after intratracheal injection in rats (Vorwald, 1953; Vorwald et al., 1955; Schepers et al., 1957; Schepers, 1961; Vorwald et al., 1966; Reeves et al., 1967; Reeves and Deitch 1969; Spencer et al., 1968 and 1972; Wagner et al., 1969; Groth et al., 1980; Ishinishi et al., 1980) and perhaps in monkeys (Schepers, 1964; Vorwald et al., 1966; Vorwald, 1968; but see also Wagner et al., 1969 for negative evidence). No pulmonary tumors were produced in rabbits (Vorwald, 1950), hamsters (Wagner et al., 1969), and guinea pigs (Vorwald, 1950; Schepers, 1961; Reeves et al., 1972).

Bone tumors were produced by intravenous or intramedullary injection in rabbits (Gardner and Heslington, 1946; Dutra and Largent, 1950; Barnes et al., 1950; Hoagland et al., 1950; Araki et al., 1954; Janes et al., 1954 and 1956; Kelly et al., 1961; Yamaguchi, 1963; Higgins et al., 1964; Tapp, 1969; and Fodor, 1977). The one nondetailed report claiming osteosarcoma in mice (Cloudman et al., 1949) needs confirmation, as does the report of osteosarcoma in rabbits after inhalation exposure (Dutra et al., 1951). Bone tumors were never observed in rats and guinea pigs.

It would appear from these data that pulmonary tumors can be obtained with beryllium in rats and perhaps in monkeys, but not in rabbits, hamsters, and guinea pigs; and that bone tumors can be obtained with beryllium in rabbits and perhaps in mice, but not in rats and guinea pigs. The negative evidence with guinea pigs is particularly strong and involves both intravenous injection (Gardner and Heslington, 1946; Vorwald, 1950) and inhalation (Schepers, 1961; Reeves et al., 1972) at levels that were definitely carcinogenic in rabbits and rats, respectively.

This apparent species specificity, which might operate with other types of carcinogenesis as well (guinea pigs are generally regarded as poor models for cancer induction), has remained thus far quite unexplored. It is certainly noteworthy that guinea pigs develop cutaneous hypersensitivity to beryllium, whereas rats do not (Reeves, 1978). In rabbits, the spleen has been found to be involved in the neoplastic response to intravenous beryllium. Gardner and Heslington (1946) observed prompt splenic atrophy in beryllium-injected rabbits; Janes et al. (1954) found that the splenic atrophy afflicted only those animals that developed the osteosarcomas, whereas the nonresponding animals had a normal-looking spleen. In a later work, Janes et al. (1956) could increase the yield of osteosarcomas in beryllium-injected rabbits twice by performing splenectomy. These studies allow the working hypothesis that some form of cellular immunity, with the immunocompetent cells arising from the spleen, may be a factor in determining whether the response to beryllium will be neoplastic or not, and that various species, or perhaps various members of one species, have resistance to beryllium cancer according to their immunocompetence.

7.1.8.3 Carcinogenic Forms and Dose-Response Relationships--There is insufficient evidence to implicate any specific chemical form of beryllium as the exclusive carcinogenic entity. Ionic beryllium changes to beryllium hydroxide upon inhalation, and both forms, upon inhalation or intratracheal injection, respectively, have caused pulmonary tumors in rats (Vorwald, 1953; Schepers et al., 1957; Reeves et al., 1967; Groth et al., 1980). There is reason to believe that beryllium hydroxide particles can change to beryllium oxide upon aging (Reeves, in press). Beryllium oxide, when directly introduced into the lungs of rats, showed a remarkable pattern of carcinogenicity, clearly indicating that firing temperature had a definite influence on the tumor yield and that only "low-fired" (500°C) beryllium oxide was highly carcinogenic (Spencer et al., 1968, 1972). Sanders et al. (1978) observed only one case of lung tumor among 184 rats exposed to "medium-fired" (1000°C) beryllium oxide. Frequently, no tumors were obtained with beryllium oxide; however, in early studies, the type of beryllium oxide to which the animals were exposed was not generally identified (Cloudman, 1949; Dutra and Largent, 1950; Hoagland et al., 1950; Araki et al., 1954; Vorwald et al., 1966).

Experiments aiming at the establishment of a dose-response relationship with intravenous beryllium are limited. Nash (1950) suggested 12 mg beryllium/rabbit as the minimum effective total dose to produce osteosarcomas; in the experiments of Hoagland, incidence of osteosarcomas increased from 50 to 75 percent as beryllium oxide content of a fluorescent phosphor was increased from 2.3 percent to 14 percent. Barnes et al. (1950) could increase the incidence of rabbit osteosarcomas from 4/14 (29 percent) to 2/3 (67 percent) by doubling the dose of intravenous zinc beryllium silicate from 7.5 to 15 mg. However, in the inhalation experiment of Dutra et al. (1951) and in the intramedullary experiments of Yamaguchi (1963), there was no clear-cut relation between dose and tumor yield.

Vorwald et al. (1966) cited results of their own unpublished studies, according to which "almost 100 percent of a large number of rats" developed lung cancer after 18 months of exposure to 42 or 21 μg beryllium (as beryllium sulfate)/m^3; after exposure to 2.8 μg beryllium (as beryllium sulfate)/m^3, the incidence of lung cancer was 13/21 (62 percent). These figures came under considerable scrutiny during the beryllium hearings at the Occupational Safety and Health Administration (Lesser, 1977). It was pointed out that these experiments were poorly controlled and that at least the data of the exposure intended to be 2.8 μg beryllium/m^3 deserved no confidence. Wagner et al. (1969) could obtain pulmonary tumors in rats with beryl ore (beryllium content 4.14 percent) but not with bertrandite ore (beryllium content 1.4 percent). Similarly, Groth et al. (1980) obtained pulmonary tumors with beryllium metal, beryllium hydroxide, and a beryllium-aluminum alloy, with beryllium content ranging from 62 to 100 percent; whereas with other alloys, ranging in beryllium content from 2.2 to 40 percent, they obtained no tumors. Thus, the evidence points to the existence of a definable dose-response relationship in experimental beryllium carcinogenesis.

Reeves (1978) examined this relationship by the probit method. For the induction of osteosarcoma in rabbits following intravenous injection of zinc beryllium silicate, the median effective total dose per animal was 11.0 mg beryllium; the curve intersected the 1 percent incidence level at 3.8 mg, the 0.1 percent incidence level at 2.7 mg, and the 0.01 percent incidence level at 2.0 mg. For the induction of pulmonary carcinoma in rats after inhalation of beryllium sulfate (35 hours/week chamber exposure lasting 3 months or more), the median effective concentration was 18.0 μg beryllium/m^3; the curve intersected the 1 percent incidence level at 12.0 μg/m^3, the 0.1 percent incidence level at 10.5 μg/m^3, and the 0.01 percent incidence level at 9.0 μg/m^3. Obviously, these estimates are subject to considerable uncertainty.

7.1.9 Summary of Animal Studies

This section has presented a discussion of animal experiments concerning the carcinogenicity of beryllium, as summarized by Reeves (1978), Groth (1980), and Kuschner (1981). These studies are listed in Table 7-8.

Experimental beryllium carcinogenesis was successfully accomplished by intravenous or intramedullary injection of rabbits and, perhaps, of mice; and by inhalation exposure or intratracheal injection of rats and, perhaps, of monkeys and rabbits. Not susceptible to beryllium carcinogenesis are guinea pigs and, perhaps, hamsters. This species specificity appears to be connected with immunocompetence.

In rabbits, osteosarcomas and chondrosarcomas were obtained. The tumors were highly invasive, metastasized readily, but gave variable transplant experience. They were judged to be histologically similar to corresponding human tumors. In rats, pulmonary adenomas and/or adenocarcinomas of questionable malignancy were obtained. The tumors were less invasive, and both the metastasis and transplant experiences were variable. They appeared to be histologically associated with the purulent lesions of chronic murine pneumonia.

There is some evidence that the carcinogenicity of beryllium oxides is inversely related to their firing temperature, with only the "low-fired" (500°C)

TABLE 7-8. CARCINOGENICITY OF BERYLLIUM COMPOUNDS

Year	Species	Compound	Route of Administration	Tumor	Reference
1946	rabbit	zinc beryllium silicate	intravenous	osteosarcoma	Gardner
1949	mouse	zinc beryllium silicate	intravenous	"malignant bone tumors"	Cloudman
1949	rabbit	zinc beryllium silicate	intravenous	osteosarcoma	Cloudman
1950	rabbit	zinc beryllium silicate and beryllium metal	intravenous	osteosarcoma	Barnes, Barnes, Sissons
1950	rabbit	zinc beryllium silicate	intravenous	osteosarcoma	Hoagland
1950	rabbit	beryllium oxide and zinc beryllium silicate	intravenous	osteosarcoma	Dutra
1951	rabbit	beryllium oxide	inhalation	osteosarcoma	Dutra
1953	rat	beryllium sulfate tetrahydrate	inhalation	lung cancer (adeno and squamous)	Vorwald
1954	rabbit	beryllium phosphate beryllium oxide	intravenous	osteosarcoma	Araki
1954	rabbit	zinc beryllium silicate	intravenous	osteosarcoma	Janes
1957	rat	beryllium sulfate tetrahydrate	inhalation	lung cancer (adeno and squamous)	Schepers
1961	rabbit	zinc beryllium silicate	intravenous	osteosarcoma	Kelly
1964	rabbit	zinc beryllium silicate	intravenous	chondrosarcoma	Higgins
1964	rabbit	zinc beryllium silicate	intravenous	osteosarcoma	Peterson

(continued on the following page)

TABLE 7-8. (continued)

Year	Species	Compound	Route of Administration	Tumor	Reference
1965	rat	beryllium sulfate tetrahydrate	ingestion	? no greater than controls	Schroeder
1966	monkey	beryllium oxide	intratracheal instillation	pulmonary cancer (anaplastic)	Vorwald
	monkey	beryllium sulfate tetrahydrate	inhalation	pulmonary cancer	Vorwald
1967	rat	beryllium sulfate tetrahydrate	inhalation	lung-cancer (alveolar-adeno Ca)	Reeves
1968	rabbit	beryllium oxide	intravenous	osteosarcoma	Komitowski
1969	rat	beryl ore bertrandite ore	inhalation	lung cancer (adeno) no tumors	Wagner
1969	hamster	beryl ore bertrandite ore	inhalation	none none	Wagner
1969	monkey	beryl ore bertrandite ore	inhalation	none none	Wagner
1969	rabbit	zinc beryllium silicate beryllium silicate beryllium oxide	subperiosteal injection	osteosarcoma osteosarcoma osteosarcoma	Tapp
1972	rat	beryl ore beryllium oxide beryllium hydroxide beryllium metal	intratracheal	pulmonary tumors pulmonary tumors pulmonary tumors pulmonary tumors	Groth
1975	rat	beryllium fluoride beryllium chloride	inhalation	lung cancer (adeno and squamous)	Lituinov

(continued on the following page)

TABLE 7-8. (continued)

Year	Species	Compound	Route of Administration	Tumor	Reference
1975	rabbit	zinc beryllium silicate	intramedullary	osteosarcoma	Mazabraud
1977	rat	beryllium sulfate tetrahydrate	ingestion	? no greater than controls	Morgareidge
1978	rat	beryllium oxide	inhalation	single lung cancer (adeno)	Sanders
1979	rat	beryllium metal beryllium alloy passivated beryllium metal beryllium hydroxide	intratracheal instillation	lung cancer (adeno and squamous) " "	Groth
1980	rat	beryllium oxide	intratracheal instillation	lung cancer (squamous, adeno, lympho)	Ishinishi

Source: Adapted from Kuschner (1981)

variety presenting a substantial hazard. Limited dose-response evidence indicates about 2.0 mg beryllium (as beryllium oxide) as the minimum intravenous dose for production of osteosarcomas in rabbits, and about 10 μg beryllium (as beryllium sulfate)/m^3 as the minimum atmospheric concentration for production of adenocarcinomas in rats.

Although some studies involving beryllium clearly have limitations, the totality of the data, using the criteria of the International Agency for Research on Cancer (IARC), requires that beryllium be placed in the "sufficient evidence" category of animal carcinogens.

7.2 EPIDEMIOLOGIC STUDIES

7.2.1 Bayliss et al. (1971)

The first in a series of government-sponsored studies of cancer in workers exposed to beryllium was accomplished by Bayliss et al. (1971). This cohort mortality study consisted originally of some 10,356 former and current employees of the beryllium-processing industry (two companies in Ohio and Pennsylvania) of which 2,153 had to be excluded because insufficient information was available with regard to these workers. Records consisted entirely of lists of names only with approximate years of employment of individuals who were presumably employed at the Brush Beryllium Company prior to 1942. No other information was available on these workers from company employment records at the time after an intensive search was completed. These lists were prepared by an earlier Brush Beryllium Company physician who is now deceased. After the additional removal of another 1,130 females, the study was left with 6,818 males. Of this number, 777 deaths occurred from January 1, 1942, to the end of the cut-off date, December 31, 1967, compared to 842.4 expected deaths based upon U.S. male death rates--a shortfall attributable to the "healthy worker effect." Only a slightly elevated risk of lung cancer (International Classification of Diseases [ICD] 160-164) was evident overall (36 observed versus 34.06 expected). No significant risk of lung cancer was found to exist in relation to length of employment, beginning date of employment, or kind of employment (office versus production), nor were significant risks of other forms of cancer evident from these data.

This study suffers from several deficiencies, not the least of which is the fact that over 2,000 individuals had to be eliminated from the study because data regarding birth date, race, and sex could not be obtained for them. The author indicated that this reduction in the size of the study necessitated the elimination of some 251 deaths, and represented a loss of over 20 percent of the cohort and 25 percent of the known deaths, a circumstance that had the potential for introducing considerable bias into the results.

A second major problem with the study is the fact that it did not analyze the data according to length of time since initial employment in the industry. The lack of such an analysis meant that questions dealing with latency could not be addressed in the study.

A third deficiency is that the populations of several different plants were combined into one cohort for the study. As a result, the study failed to consider the many potential differences of exposure levels in different plants. Individuals were studied in groups according to their beginning dates and durations of employment, despite the fact that their exposure histories may have been totally dissimilar.

For the above-cited reasons, this study was deemed not useful for the evaluation of cancer mortality in beryllium-exposed workers.

7.2.2 Bayliss and Lainhart (1972, unpublished)

In an attempt to remedy the deficiencies of their earlier study, Bayliss and Lainhart (1972), in an unpublished study presented at the American Industrial Hygiene Association meeting on May 18, 1972, narrowed the scope of study to only one beryllium-processing company, which had seemingly complete employment records for two locations in Pennsylvania. This change effectively reduced the size of the cohort to some 3,795 white males, while retaining the same starting date and cut-off date as was used in the earlier study. In the 1972 version of the study, Bayliss et al. found that 601 members of the cohort had died, as compared to 599.9 expected deaths based on period- and age-specific U.S. white male death rates. Again, no significant excess of unusual mortality from any cause was evident. For lung cancer (ICD 160-164) overall, 25 deaths were observed versus 23.69 expected. Even when latency was considered, no significant excess risk of lung cancer was apparent after a lapse of 15 years from initial exposure, at which time 14 deaths were observed versus 13.28 expected. In addition, no significant risks were apparent in relation to intensity of exposure, duration of exposure, or beginning date of employment. The Bayliss and Lainhart (1972) study was criticized by Bayliss and Wagoner (1977) in a third version of the study, which was submitted to the Occupational

Safety and Health Administration (OSHA) as part of the beryllium standards development process. In this criticism, the earlier paper was said to have multiple limitations, among which were the following: 1) the study included clerical and administrative workers who presumably had not been exposed to beryllium; 2) the data were obtained from industrial representatives, which precluded an independent assessment of plant employment files to ensure that all potentially exposed workers were included; and 3) the study did not assess latency 20 or more years after initial employment, although it did examine mortality after a 15-year lapse.

7.2.3 Bayliss and Wagoner (1977, unpublished)

This third version of the Bayliss et al. study was reduced in size to a cohort mortality study of workers employed at only one of the original company's plants. The cohort studied was composed of 3,070 white males, who were followed until January 1, 1976. Vital status was unknown for only 80 members of the cohort (3 percent), and these individuals were considered to be alive until the end of the study's cut-off period. Altogether, 884 deaths were observed, as compared to 829.41 expected deaths based on period- and age-specific U.S. white male death rates. A significant excess of lung cancer was noted (ICD 162-163), with 46 cases observed versus 33.33 expected ($P < 0.05$). A significant excess of heart disease was also noted (399 observed versus 335.15 expected, $P < 0.05$), as was a significant excess of nonmalignant respiratory disease (32 observed versus 19.02 expected, $P < 0.01$). Irrespective of duration of employment, a significant excess was noted in bronchogenic cancer following a lapse of 25 or more years since initial employment.

In the Bayliss and Wagoner (1977) study, the authors discussed for the first time the impact of cigarette smoking as a possible confounding agent contributing to the excess risk of lung cancer. An examination of the results of a cross-sectional health examination survey conducted at the plant under study by the U.S. Public Health Service (PHS) in 1968 revealed little difference in the cigarette-smoking patterns of the surveyed employees, as compared to smoking patterns in the United States as a whole, determined from a health interview survey conducted by the PHS from 1964 to 1965. An increase in the percentage of heavier smokers was indicated in the 1968 survey, as compared with national data (21.4 versus 15.3 percent). Because of the results just cited, cigarette smoking was dismissed by the authors as the cause of the increased risk of bronchogenic cancer and other diseases in the cohort under study. Dismissing the role of cigarette smoking as a contributing cause of the excess risk of lung cancer may have been unwarranted for several reasons. First, the smoking patterns of the 379 current employees surveyed in 1968 were probably not the same as those of the entire cohort of 3,795, which included current employees and past employees from as early as 1942. Second, the first national reports of smoking as a cause of lung cancer were produced in 1964 and were accompanied by a great deal of media attention. By 1968, intense media coverage dealing with the health consequences of smoking probably produced a diminution of cigarette smoking among various subgroups of the population in the 4-year interim period between surveys. Furthermore, while the 1968 survey done at the plant did speak of current cigarette-smoking patterns, the issue of prior cigarette smoking was not addressed, nor was the issue of pipe smoking and cigar smoking. Additional criticisms of the Bayliss and Wagoner (1977) study, as well as subsequent iterations of the same study, including the final version (Wagoner et al., 1980), are discussed in the following review.

7.2.4 Wagoner et al. (1980)

Wagoner et al. (1980) reduced slightly the cohort of Bayliss and Wagoner (1977) to a smaller cohort mortality study of 3,055 white males employed at some time between January 1, 1942 and December 31, 1967, in the same beryllium-processing facility. The results showed a significantly high risk of lung cancer (47 observed versus 34.29 expected, $P < 0.05$) for those individuals followed until December 31, 1975. This excess extended to members of the cohort followed for more than 24 years since initial employment (20 observed versus 10.79 expected, $P < 0.01$). When the analysis was confined to those whose initial employment occurred prior to 1950, but who were followed for 15 years or more from date of initial employment, a significantly high risk of lung cancer was apparent (24 observed versus 13.42 expected, $P < 0.05$). In fact, no deaths from lung cancer were observed in anyone whose initial employment occurred after 1950 (0 observed versus 2.03 expected). The authors concluded that this excessive risk of lung cancer "could not be related to an effect of age, chance, self-selection, study group selection, exposure to other agents in the study facility, or place of residence."

This study has received severe criticism from several sources: an internal Center for Disease Control (CDC) Review Committee appointed to investigate defects in the study, several professional epidemiologists (MacMahon, 1977, 1978; Roth and Associates, 1983), and also one of the study's co-authors (Bayliss, 1980). These researchers have criticized Wagoner et al. for inadequately discussing all qualifiers that might explain any of the significant findings of their study.

The cohort studied in Wagoner et al. (1980) was composed of workers at the facility who had been employed prior to December 31, 1967, based on the facility's employment records and the results of a cross-sectional medical survey done in 1968 at the plant. The cohort excluded employees who were not directly engaged in the extraction, processing, or fabrication of beryllium, or in on-site administrative, maintenance, or support activities. The numbers of expected deaths used in the study were based on U.S. white male death rates that had been generated by an analytic life table program designed by the National Institute for Occupational Safety and Health (NIOSH). As a basis for these calculations, the program used actual U.S. deaths recorded by cause, age, race, sex, and year through 1967, together with census population data from 1941 to 1967. These data were provided by the Bureau of the Census and the National Center for Health Statistics. Unfortunately, at the time of this study and subsequent studies on beryllium, cause of death information was not available from these agencies on a year to year basis after 1967. As a result the NIOSH life table program could not generate death rates during this period without the application of certain assumptions. In order to estimate expected deaths during the period from 1968 through 1975, death rates were assumed by the authors to be unchanged from those generated by the NIOSH life table program for the period from 1965 through 1967. The result was that for causes of death with declining death rates, expected deaths were overestimated, with a resultant underestimate of risk. Similarly, for those causes with increasing death rates during the interval studied, expected deaths were underestimated, with a resultant upward risk bias, as was the case with respect to all of the lung cancer risk calculations made by the authors. After this problem had been corrected by the inclusion of actual lung cancer mortality data for the period in question, expected lung cancer deaths were recomputed prior to the publication of the Wagoner et al. (1980) study by Bayliss (1980). The result was an increase from 34.29 to 38.2 expected lung cancer deaths, or an excess of 11 percent. This correction in itself was enough to eliminate the statistical significance calculated by Wagoner et al. in their overall lung cancer tabulation. With respect to latency, the risk of lung cancer was reduced to one of only borderline significance in the cohort subgroup that was observed for 25 years or more after initial employment. These corrections have been confirmed as correct by Richard Monson (MacMahon, 1977, 1978), following a reanalysis of the NIOSH data tapes in an independent Monson life table program at Harvard University.

Wagoner et al. found 875 deaths in their cohort. The vital status of 79 members of the cohort remained unknown as of December 31, 1975. The authors' assumption was that these individuals would be counted as alive until the end of the study, and that because of their added person-years, any finding of increased cause-specific mortality would tend to be underestimated. Actually, these 79 individuals represented only 2 percent of the total cohort, and any additional person-years included from the time when they were last known to be alive would have added little to the number of expected deaths. Furthermore, given the intense scrutiny afforded this population in determining vital status by both Wagoner and Mancuso in their own studies of the same workers, and considering the fact that these researchers shared information on newly found lung cancer deaths, it is questionable whether any additional lung cancers would have been found, either in the 79 individuals with unknown vital status, or in the 15 known dead for whom causes of death were not known by the study's cut-off date. The latter number was reduced to 10 in subsequent tabulations, after information on causes of death was located for five individuals (Bayliss, 1980). None of these were lung cancer.

Additional factors that could have contributed to the finding of an excess risk of lung cancer in Wagoner et al. (1980) are as follows:

1) One lung cancer victim was added to the cohort by Wagoner based upon a single 4" by 7" personnel card that listed the same day (June 1, 1945) as the "starting date" and "release date" in the plant. In actuality, the individual, according to company sources, never reported for work because a preemployment chest X-ray revealed a lung abnormality. The company paid him for the time he was being examined, which is why his name and social security number appeared on a social security earnings report. Bayliss excluded him from his original cohort based on the information on the same personnel record that said "did not pass chest X-ray."

2) In a supplemental summation on the epidemiology of beryllium with respect to the proposed occupational safety and health standard for exposure

to beryllium (January 13, 1978; prepared by Roth and submitted by Brush Wellman), it states that 295 white males, who were employed at the Reading plant of Kawecki-Berylco Industries, in jobs similar or identical to those of the Wagoner et al. cohort were not included. Of that group the report states that 199 had a known vital status. One hundred eighty-one were alive and 18 deceased by the close of the study period. Dr. Roth's post hearing statement indicated that the inclusion of these additional employees would have increased the cohort by about 10 percent.

3) In researching the medical files of the 47 lung cancer victims, David Bayliss, one of the co-authors, discovered that 23 files contained information to the effect that the individuals in question were smokers. In addition, the company from which the cohort was derived provided data indicating that 33 of the 47 lung cancer victims (70 percent) smoked cigarettes, based on a company-sponsored survey by Hooper-Holmes (Kawecki-Berylco Industries (KBI), 1977). Bayliss determined that of the 47 cases, a total of 42, or better than 89 percent, smoked cigarettes, based on a combination of smoking information gathered by the company and smoking information from the medical files. If this information is accurate, it could indicate the presence of a confounding effect due to cigarette smoking. Bayliss further established that one of the remaining 5 cases died from another cause of death. This victim actually died from a glioblastoma multiforme (astrocytoma) of the brain, according to medical data. However, his death certificate incorrectly listed lung cancer as an underlying cause of death. If the 47 cases are reduced to 46, then 91 percent smoked cigarettes.

4) An inadequate discussion was presented on the confounding effects of exposure to potential carcinogens prior to and following employment in the beryllium industry. These factors are especially important since the authors maintain that only short-term employees are affected. Evidence from employment records, medical files, questionnaires administered during the 1968 NIOSH-sponsored medical survey of the plant, and death certificates indicates a distinct possibility that these factors are significant in the cohort under study (Bayliss, 1980).

Another problem with the Wagoner et al. (1980) study, as stated by the authors themselves, is that the expected deaths were overestimated by 19 percent because of the use of death rates for white males in the United States as a whole, rather than those for Berks County, Pennsylvania, where the plant was located. This statement was based on a comparison in Mason and McKay (1973) of the 1950-1969 age-adjusted lung cancer death rate for white males in Berks County, Pennsylvania, with that of the 1950-1969 age-adjusted lung cancer rate for white males in the U.S. (Mason and McKay, 1973). Actually, this reference by Wagoner et al. to "lower" Berks County rates as a justification for the position that the expected deaths based upon national rates are overestimated, has been criticized by Roth and Associates (1983) as well as by Bayliss (1980). Bayliss' criticism cited the fact that the periods of observation were different, i.e., that the Mason data covered the period from 1950 through 1969, while that of Wagoner et al. (1980) covered the period from 1942 through 1975. Bayliss also pointed out that to derive reliable county death rates from the existing data would be extremely difficult to do with any confidence. Roth and Associates criticized the use of Berks County rates as not being reflective of greatly elevated lung cancer death rates for the City of Reading, which they maintained were 12 percent higher than the national rates. According to Roth and Associates (1983), 46 percent of the workers employed by the plant in 1968 resided within the city limits, whereas only 34 percent of Berks County residents (1970) resided within the city; and therefore, death rates calculated for Berks County should be weighted toward the relatively higher City of Reading rates. This adjustment would have the effect of generating comparison lung cancer rates that are perhaps greater than U.S. rates, and would consequently increase the number of estimated expected deaths.

Wagoner et al. (1980) also claim to have noted an unusual histopathologic distribution of cell types in the cases of 27 of the 47 lung cancer deaths for which pathologic specimens could be obtained. Adenocarcinomas were noted in 8 cases (32 percent) out of 25 individuals histologically confirmed to have died from bronchogenic carcinoma (Smith and Suzuki, 1980). Wagoner et al. apparently disregarded the conclusion of Smith and Suzuki that "the prevalence of histopathologic cell types of bronchogenic carcinomas among beryllium-exposed workers could not be presently defined." Smith and Suzuki attributed their conclusion to the fact that there was "an inadequate response rate for the submission of pathology specimens for review," since tissue specimens were not available for 43 percent or 20 of the total number of lung cancers. Wagoner et al., however, citing data from earlier studies (Haenszel et al., 1962; Axtell et al., 1976) to the effect that the frequency of adenocarcinomas in U.S. white males was 15 or 16 percent, concluded that a significant "shift" of histologic cell types was apparent in lung cancer deaths in beryllium workers. However, an internal NIOSH memorandum (Smith, 1978) stated that more recent data by Vincent et al. (1977) indicated that a shift in the prevalences of histopathological cell types of lung cancer in the general population over time has led to an increase in the prevalence of adenocarcinoma to 24 percent, and therefore the prevalence of adenocarcinomas in the lung cancer deaths of beryllium workers is not significantly different from that expected. Smith suggested in his memorandum that any mention by Wagoner et al. of the histopathological examination of lung tumor specimens that does not take into consideration the unrepresentative nature of the specimens should be deleted from the paper.

To summarize, it appears that the authors of the Wagoner et al. (1980) study tended to exaggerate the risk of lung cancer in a population of workers potentially exposed to beryllium, and underemphasized or did not discuss sufficiently the shortcomings of the study. The net effect was to turn a "suggested association" of lung cancer with beryllium exposure into a questionable "significant association." However, despite the study's problems, there still remains a possibility that the elevated risk of lung cancer reported therein was due in part to beryllium exposure, and therefore, the CAG considers the study to be suggestive.

7.2.5 Infante et al. (1980)

In a companion paper by Infante et al. (1980) which appeared in the same journal as the Wagoner et al. (1980) study, lung cancer mortality was studied by the retrospective cohort method in white males for whom data had been entered into the Beryllium Case Registry (BCR) with diagnoses of beryllium disease. A person was adjudged to have beryllium disease and thus to be eligible for inclusion into the BCR if three or more (two were mandatory) of the following five criteria were met (Hasan and Kazemi, 1974).

Mandatory -- (1) Establishment of significant beryllium exposure based on sound epidemiologic history.
(2) Objective evidence of lower respiratory tract disease and a clinical course consistent with beryllium disease.
Mandatory -- (3) Chest X-ray films with radiologic evidence of interstitial fibronodular disease.

(4) Evidence of restrictive or obstructive defect with diminished carbon monoxide diffusing capacity by physiologic studies of lung function.

(5) 1 - Pathologic changes consistent with beryllium disease on examination of lung tissue.

2 - Presence of beryllium in lung tissue or thoracic lymph nodes.

Close to 900 individuals have been entered into the BCR as of the present date, based in some measure on evidence of non-malignant respiratory disease objectively determined by appropriate and established medical procedures (Mullan, 1983).

According to Mullan (1983), the criteria listed above are characterized by high sensitivity but low specificity in that, while they are able to identify cases of actual beryllium disease, they can also lead to the inclusion of non-beryllium disease cases; in particular, cases of sarcoidosis.

Infante et al. eliminated from their cohort all nonwhite and female subjects because of their lack of "statistical sensitivity," and also eliminated all subjects who were deceased at the time of the BCR entry. The authors maintain that this constraint was necessary in order to ensure that no bias would result from the "selective referral of individuals with the outcome still under investigation," i.e., individuals with lung cancer. The use of the above procedure, however, raises the question that such a self-imposed constraint may not have prevented the "selective referral" of lung cancer victims prior to their deaths. This possible effect might have been eliminated if the above-referenced limitation had been applied to such cases as well. Or, alternatively, it should perhaps have been assumed that no potential bias existed, and that therefore all BCR cases added posthumously should have been retained.

Altogether, Infante et al. included in their study cohort only 421 members of the BCR, less than 50 percent of the total. Of these, vital status could not be determined on 64 (15 percent), while 139 (33 percent) were found to have died by December 31, 1975. In this latter group, the causes of death could not be ascertained for 15 individuals. These were placed in an "undetermined cause of death" category. The authors ceased accumulating person-years on the group of 64 with unknown vital status at the time each was last known to be alive instead of to the end of the study. This procedure served to reduce expected mortality slightly in every cause category. This reduction was offset, however, by the fact that no potential deaths that might have occurred during this time up to the cut-off date in this group of 64 cases were included. With the intense scrutiny given the issue of lung cancer and beryllium by Infante and the many research investigators who have worked with the BCR since its inception (including Wagoner, Bayliss, and Mancuso), it is questionable whether any of the 15 deaths from undetermined causes, or any of the 64 cases with unknown vital status, were lung cancer deaths. Hence, it is probable that the estimated lung cancer risk is somewhat overestimated by this procedure.

Additionally, since the same National Institute for Occupational Safety and Health (NIOSH) life table program that was used to calculate lung cancer deaths in the Wagoner et al. study was the method used to derive expected lung cancer deaths in the Infante et al. study, it was subject to the same problems as mentioned previously, i.e., a +11 percent error in the calculated expected lung cancer deaths. If it is assumed that this distortion is of the same magnitude as that described in the discussion of the Wagoner et al. (1980) study, the SMR of the Infante et al. (1980) study would be inflated by 11 percent also.

As expected, Infante et al. (1980) found a significantly high excess risk of "non-neoplastic" respiratory disease (52 observed deaths versus 3.17 expected). In terms of total cancer, 19 deaths were observed versus 12.41 expected. With respect to lung cancer, 6 deaths occurred more than 15 years after the onset of beryllium exposure, versus 2.81 expected ($P < 0.01$). If the expected deaths are adjusted upwards by 11 percent to compensate for the overestimate produced by the NIOSH life table program, the authors' P value is reduced to one of borderline significance (6 observed versus 3.12 expected deaths; $P < 0.09$).

Infante et al. divided their cohort on the basis of "acute" versus "chronic" beryllium disease. Subjects were considered "acute" if the BCR records indicated a diagnosis of chemical bronchitis or pneumonitis or other acute respiratory illness at time of entry into the registry. Subjects were called "chronic" if BCR records indicated a diagnosis of pulmonary fibrosis or some recognized chronic lung condition at time of entry into the registry. All other cases, if they could not be designated as chronic, were considered by Infante to be acute if the onset of the disease occurred within one year of initial exposure.

These definitions should not be confused with the medically accepted definitions of acute and chronic beryllium disease, in which cases of beryllium disease lasting one year or less are termed "acute," while those lasting longer than one year are termed "chronic." The authors found no significant lung cancer, not even an excess in their "chronic" respiratory disease group of 198 persons (1 observed death versus 1.38 expected). However, in their "acute" respiratory disease group, they found 6 observed lung cancer deaths versus 1.91 expected ($P < 0.05$), and in the interval of more than 15 years since initial onset of beryllium exposure, 5 observed lung cancer deaths were found versus 1.56 expected ($P < 0.05$). These findings, however, suffer from the same problems previously alluded to regarding the NIOSH life table program, and must therefore be regarded as questionable with respect to their implications.

The possibility cannot be discounted that cigarette smoking may have contributed to an excess risk in the Infante et al. (1980) study, despite the authors' claim that cigarette smoking is unlikely to have played a role in the somewhat increased lung cancer risk they found. Although the criteria for inclusion in the BCR have been evolving and undergoing revision to improve their sensitivity and specificity since the Registry's inception in 1952, it is possible that in the early years of the Registry, the criteria could have allowed the inclusion of individuals with respiratory disease either brought on by or exacerbated by cigarette smoking. Such individuals would then have been likely candidates for selection into the BCR. Of the seven lung cancer cases discussed by Infante et al. (1980), six were admitted to the hospitals for treatment before 1955, and one was admitted in 1964. The ability to detect subtle radiographic changes consistent with a diagnosis of beryllium disease was relatively undeveloped in the early 1950s. Given current practices in the interpretation of X-rays and pulmonary function data, such a misdiagnosis would be unlikely today.

Any one of the factors referred to above could have been of sufficient magnitude to produce a significant excess lung cancer risk in the group under study. The authors' treatment of these confounders serves to exaggerate this risk without presenting any compensating negatives. It appears likely that correcting or controlling the influence of two or more of these factors could reduce the estimated risk calculated to one of nonsignificance. The findings of Infante et al. (1980) are thus seen to be, at best, only suggestive of an increased risk of lung cancer from exposure to beryllium.

7.2.6 Mancuso and El-Attar (1969)

The first in a series of four epidemiological studies of mortality in workers exposed to beryllium was conducted by Mancuso and El-Attar (1969) on the same study population as was used in the Bayliss and Wagoner studies. The cohort in the Mancuso and El-Attar study, however, was derived from quarterly earnings reports provided by the Social Security Administration. Quarterly earnings reports on every employee of a given company covered by social security are filed four times a year by all companies included under the Social Security Act. These reports generally consist of lists of names, social security numbers, dates of birth, and reported earnings during the quarters for which filing is done. With respect to beryllium, Mancuso and El-Attar obtained quarterly earnings reports for both companies studied by Bayliss et al. and Wagoner et al., but limited their study to the period of employment from 1937 to 1948. Altogether, they identified 3,685 white males from two beryllium plants. Only 729 white males were found to have died through the year 1966. Included in this group were 31 lung cancers (ICD 162-163). The authors contrasted internally generated age-, plant-, and period-specific death rates by cause with internally generated age-specific death rates by cause from an "industrial control." Unfortunately, because of the small numbers involved, the authors did not include any employees of age 55 or over. The industrial cohort used for purposes of comparison was not identified. The 729 deaths were distributed into 160 narrow subcategories, based on four broad age groups, two companies, four periods of time, and five broad death categories. Internal death rates were computed in each subcategory. Because the numbers from which these internal rates were derived are so small (in some instances nonexistent) from one subcategory to another, the comparisons with 20 rates generated from the industrial control are shaky at best and appear to vary considerably. No trends are evident. No significance tests were done. The data are open to interpretation. The authors themselves conclude, based on their analysis, that their data are "severely limited" with respect to answering the question of carcinogenic risk.

7.2.7 Mancuso (1970)

In the second study of the same cohort, Mancuso (1970) added duration of employment as a variable, and divided his cohort into a 1937-1944 component and a 1945-1948 component, by dates of initial employment. Both subgroups were followed until 1967, and internal death rates were computed based upon a technique the author terms "the generation cohort method." Each cohort was classified into 10-year age groups, beginning with 1940. An average annual mortality rate was calculated by age as of 1940. Age adjustment was done through the direct method, using the 1950 standard million as a base population (presumably the U.S. 1950 standard million, although the author does not state what his comparison population is). Comparisons were internal by gradient of exposure as defined by duration of employment and by evidence of prior chemical respiratory disease.

A higher rate of lung cancer was noted by the author among workers whose first employment occurred during the period 1937-1944 in age category 25-64, and who were employed for 5 or fewer quarters (99.9 per 100,000) compared to those employed 6 quarters or longer (33.2 per 100,000) based on 16 and 4 lung cancers, respectively. He further found a higher rate in one company among a group of workers with histories of chemical respiratory illness versus those who did not have this condition. One hundred forty-two white males with respiratory illness during the period 1940-1948 were identified in this plant. Out of a total of 35 deaths occurring to this group, 6 were due to lung cancer. Based on these 6 lung cancers, an age-adjusted lung cancer death rate of 284.3 per 100,000 was calculated, compared to an age-adjusted rate of 77.7 per 100,000 (based upon 9 lung cancer deaths) in the total cohort of this company's workers employed from 1937 to 1948. These calculations were confined to individuals who were in the age group 25 to 64 in the year 1940. For some unknown reason, the author neglected to include the age group of 15 to 24, the inclusion of which would have had the effect of increasing the lung cancer death rate in individuals without prior respiratory illness by the addition of two lung cancer deaths, while leaving the rate unchanged in those with respiratory illness, thus narrowing the difference between the two rates. No significance tests were done, and the observations were based upon small numbers, as was pointed out by the author.

Although Mancuso found elevated risks in these groups, the results are subject to considerable variability. Mancuso criticized his own study for several alleged deficiencies. Some of these criticisms seem inappropriate, while others appear valid for this study and also for later studies by Mancuso of this same population. The deficiencies, according to Mancuso, consisted of "the marked influence of labor turnover on duration of employment, perhaps induced by the presence of respiratory disease; the inability to define the specific populations by department, process, or by type or form of beryllium exposure; the presence of competing causes of death; and the shortness of the period of observation." Other potential problems with these data, which were not mentioned by the author, are a lack of consideration of the effects of smoking and the effects of exposure to potential carcinogens in other jobs the workers may have had before and after their exposure to beryllium, since the suggested increase appeared only in "short-term employees." This is discussed further in a later description of the study (Mancuso, 1979). The author's conclusion that prior chemical respiratory illness influenced the subsequent development of lung cancer among beryllium workers may be somewhat overstated, in view of the many limitations of the study.

7.2.8 Mancuso (1979)

In a third update of an epidemiologic study of white male workers employed at two beryllium-manufacturing companies in Ohio and Pennsylvania, Mancuso (1979) conducted a cohort mortality study in which he divided his cohort into two subgroups, each consisting of former and current employees of the respective companies. Employees were included in the study if they had worked at any time during the period from 1942 to 1948. The original source documents, from which names and social security numbers were derived to form the cohort, consisted of quarterly earnings reports submitted to the Social Security Administration. The Ohio cohort consisted of 1,222 white males, of which 334 were deceased. The Pennsylvania cohort consisted of 2,044 white males, of which 787 were deceased. A life table analysis was performed by NIOSH, utilizing U.S. white male age- and period-specific rates (5-year age groupings) to generate expected lung cancer deaths (ICD 162, 163) through 1974 for the Ohio cohort, and through 1975 for the Pennsylvania cohort. An excess risk of lung cancer appeared in the Ohio employees after a lapse of 15 years from the onset of employment (22 observed versus 9.9 expected, $P < 0.01$). The same was true for the Pennsylvania employees (36 observed versus 22.0 expected, $P < 0.01$) following a similar latent period. The author noted that this risk was confined principally to workers with less than one year's duration of employment in the industry. No significant excess risk was noted in workers of either plant who were employed for more than five years in the industry. The author concluded, on the basis of this study and the Wagoner et al. (1980) study, that "there is evidence that beryllium causes cancer in man."

Several questions must be considered before these conclusions can be accepted as valid. These data, although derived from social security quarterly earnings reports and not from personnel records, are not independent of the data set utilized in the Wagoner et al. (1980) study. Both sets of data were analyzed through the use of the NIOSH life table program. The expected deaths generated in both studies are subject to the same influences introduced by the use of the same life table program, and by the use of the same comparison rates (U.S. white male lung cancer rates). In addition, the extensive cooperation between Mancuso (at the University of Pittsburgh) and Wagoner (at NIOSH) in the search for causes of death in the respective cohorts for study, contributed to the inclusion of lung cancer deaths known to one but not the other in both studies. As mentioned previously, because of the use of the NIOSH life tables in the Mancuso study, the calculation of expected lung cancer deaths was on the high side (approximately 11 percent) because of the same artifact involving the calculation of lung cancer rates for which the Wagoner et al. (1980) study was criticized. Hence, these results should not be considered independent of the results of the Wagoner study.

Another problem with this cohort is the use of social security quarterly earnings reports to constitute a cohort of potentially exposed employees. These files, for the most part, are limited with respect to the data available. Only the full name, social security number, and amount paid into the system each quarter of any given year are provided, and only for covered employees. An examination of microfilmed records of the reports maintained by the Social Security Administration shows that there is no possibility of determining from the reports what jobs these individuals performed for the companies, where their job stations were located, whether their jobs were on or off the premises, or whether they had actually been exposed to beryllium, or even precisely when during the 3-month period they actually started work. And, of course, these records give no information on workers who were not covered by the Act. Furthermore, in the period prior to 1942, the social security system was in the process of being established, and tremendous logistic problems in setting up the system were being encountered during this time. Because the system was not fully functional until 1942, millions of employees throughout the country did not get social security numbers until after that date. Large numbers of employees refused to join the system because they considered it to be "welfare," and many more simply reported their social security numbers inaccurately if at all when applying for work. Thus, questions remain concerning the validity of this cohort.

Another difficulty with the Mancuso (1979) study, as with his earlier studies, is a lack of discussion of other exposures these workers may have received. The author observed that the main effect (lung cancer) occurred in short-term employees more than 15 years after initial employment. These workers had an opportunity to be exposed to other potential carcinogens at jobs they may have held prior to or immediately following their short employment in the beryllium industry. This is a distinct possibility because the beryllium-manufacturing companies are located in or near heavily industrialized areas of Ohio (Cleveland, Toledo) and Pennsylvania (Reading). Roth and Associates (1983) report the presence of several industries in the Lorain, Ohio area in the period from 1942 to 1948 that conceivably could have provided an opportunity for short-term employees to receive exposure to potential carcinogens. These are as follows:

INDUSTRIES IN LORAIN AREA 1942-1948

Company	Operations	Approx. No. Employees
National Tube (now U.S. Steel)	Foundry, rolling, extruding, coke ovens	12,000
Thew Shovel	Foundry, machining, fabricating	2,000
Lorain Products	Electrical conductors, fabricating, nonferrous foundry	500
American Crucible	Structural steel parts, machining, fabricating, foundry	200
Iron Ore Ship Dock	Unloading ore	?

Another serious omission of the Mancuso (1979) study is the lack of a discussion of the effect of cigarette smoking on the target organ of interest, the lung. With respect to the question of smoking, it would appear likely that since there was considerable overlapping of this study with the Wagoner study, it is probable that most of the lung cancer victims in the Pennsylvania cohort of the Mancuso study were smokers. Hence, it is possible that cigarette smoking contributed to the increased risk of lung cancer in the Pennsylvania cohort. No information was provided in the Ohio portion of the Mancuso study regarding the smoking influence, an exposure of considerable import in lung cancer. The findings of significant excesses of lung cancer in both plants must be seen as limited because of the inadequate consideration of the confounding effects of these two likely exposures, the problem with the NIOSH life table programs, and the inadequate nature of social security quarterly earnings reports in defining an occupationally exposed cohort for study.

7.2.9 Mancuso (1980)

In the fourth update to his study of workers potentially exposed to beryllium in two beryllium-manufacturing facilities, Mancuso (1980) found statistically significant elevated risks of lung cancer in 3,685 white males employed in the period from 1937 to 1948 and followed until the end of 1976, when contrasted with viscose rayon workers. The beryllium cohort, as mentioned earlier, was derived from quarterly earnings reports filed with the Social Security Administration by the two companies. The only new addition to this latest update was the introduction of a new comparison population, that of viscose rayon workers. The source or location of these workers, however, is not mentioned by the author, who states that the "viscose rayon cohort" was derived from one company's "complete" file of microfilmed employment data on employees first hired during the period from 1938 to 1948 and followed until 1976 (a period which began one year later than that of the beryllium cohort). The origin and description of this group of workers is inadequately discussed, although the Wagoner et al. (1980) study states that the viscose rayon worker cohort utilized in the Mancuso (1980) study was located somewhere in the vicinity of the Mancuso cohort.

Lung cancer mortality experience in the beryllium cohort was contrasted with that expected based on rates specific to age and duration of employment generated from the mortality experience of the viscose rayon worker cohort. Rates were generated in two ways, the first based on the total group of employees in the viscose rayon industry, and the second based on employees with permanent assignments to only one department, according to the author. Presumably, those who exhibited mobility in their employment by moving from one department to another were excluded from the lung cancer death rate calculations in the second method. No rationale is presented by the author to explain why mortality in beryllium workers should be contrasted with expected deaths derived in these two separate ways. However, the net result was to produce two separate sets of expected lung cancer rates that differed considerably from each other. Mancuso observed 80 lung cancer deaths in his beryllium cohort of employees from the two companies combined, as compared to 57.06 expected deaths based on the former set of derived rates and 50.63 expected deaths based on the latter subset of employees working their entire time in only one department. The author did not compare his beryllium workers on the basis of time since onset of employment, but did contrast them by duration of employment. He found a statistically significant excess risk of lung cancer in employees who had been employed for one year or less, and also in employees who had been employed for four or more years by the beryllium companies. No explanation was forthcoming with respect to the choice of four years of total employment as the point at which short-term workers should be separated from long-term workers. In his earlier versions, the author utilized different durations of employment, i.e., 5 quarters (1 1/4 years) and 5-year duration of employment categories.

An interesting omission from this study is any consideration of the effects of latency according to duration of employment. It seems unusual that a discussion of this topic was not included by Mancuso, since the major output of the NIOSH life table program, which was utilized by Mancuso, is a set of tabulations by time since onset of employment. Lung cancers diagnosed within 10 years of initial exposure probably were not a consequence of that exposure. Furthermore, the designation "duration of employment" is not necessarily uninterrupted continuous employment. In reality, what is meant is "total employment" (i.e., periods of time when the employee was not exposed or not actually working, such as during layoffs and terminations, sickness, vacations, and leaves of absence between initial employment and final day of employment, are not counted by the NIOSH life table program in the category "duration of employment"). Therefore, it is possible that included in the observed deaths are the deaths of individuals who had worked only a few days for the companies, and who died from lung cancer 20 years later, as well as individuals who worked for the companies for many years continuously, but who died within five years of initial employment.

Additionally, the viscose rayon cohort appears to have been a somewhat younger population by age at hire than was the beryllium cohort (47.2 percent in the viscose rayon cohort were hired at under age 25, as compared to 38.4 percent hired at under age 25 in the beryllium cohort). Whether or not the author adjusted for age differences is questionable. Indeed, at the recent Peer Review Workshop on the Health Assessment Update for Beryllium (February,

1984) sponsored by the U.S. Environmental Protection Agency, an epidemiologist from NIOSH, Dr. Jean French, expressed concern that the Mancuso age adjustment in Mancuso's comparison of expected mortality based upon viscous rayon workers with that of actual mortality from Mancuso's beryllium cohort was "inadequate." Dr. French reported that NIOSH reanalyzed the data and found serious problems with Mancuso's analysis. Efforts to resolve this issue have not been successful through official NIOSH channels. Unsuccessful attempts to obtain the results of the analysis from NIOSH have made it difficult to determine the magnitude of impact of the required adjustment on risk estimates. Since the viscous rayon cohort was younger than the beryllium cohort, the net impact of an adjustment would be to decrease the gap between observed lung cancer deaths based upon the beryllium cohort and expected deaths based upon the viscous rayon cohort.

Another problem concerns the acquisition of cause-of-death data. Some 4.3 percent of the reported deceased members of the viscous rayon cohort remained without a cause of death, versus only 1.5 percent of the beryllium cohort. This could potentially lead to a greater underestimate of lung cancer in the viscous rayon cohort compared to the beryllium cohort if the causes of death in these two groups were fairly evenly distributed.

As in the earlier studies by the same author, a further difficulty with this study is its lack of discussion of the confounding effects of smoking and its disregard of potential exposures received not only while working for the beryllium companies, but also in jobs prior to and subsequent to employment in the beryllium industry. This represents a problem particularly because a large majority of this cohort worked for less than one year. Because the towns in which the beryllium companies were located were considerably industrialized, work in these industries could potentially have produced exposures to other known or suspected carcinogens. As an example, one of the major employers in the Lorain, Ohio area in the period from 1942 to 1948 was the National Tube Company (now U.S. Steel), whose operations involved extensive exposure to coke ovens. Nothing is revealed in the study of the origin or make-up of the viscous rayon cohort. What is known about its location comes from the Wagoner et al. (1980) study in which the authors stated that Mancuso's viscous rayon cohort was located in the vicinity of the beryllium companies.

Furthermore, since both cohorts were run utilizing the NIOSH life table program, both cohorts suffer from the previously discussed 11 percent underestimation of expected lung cancer deaths.

In conclusion, despite the author's certainty regarding the existence of a causal relationship between beryllium exposure and lung cancer, the evidence presented in this study is not convincing because of the many limitations of the study, as described above. Hence it would appear that the study is at best only suggestive of an increased risk of lung cancer due to exposure to beryllium.

7.2.10 Summary of Epidemiologic Studies

Although several studies show a statistically significant excess risk of lung cancer in individuals exposed to beryllium, all of the studies cited have deficiencies that limit any definitive conclusion that a true association exists. Support for a finding of an excess risk of lung cancer in beryllium-exposed persons consists of evidence from cohort mortality studies of two companies (Table 7-9) and one cohort mortality study of cases admitted to the Beryllium Case Registry. None of these studies can be said to be independent since all are studies of basically the same groups of workers. Extensive cooperation existed between the authors of all of these studies, even to the extent of running all cohorts through a NIOSH computer-based life table program known to produce an 11 percent underestimate of expected lung cancer deaths at the time. This problem has since been remedied. Furthermore, the authors could not adequately address the confounding effects of smoking or of exposures received during prior and subsequent employment in other non-beryllium industries in the area known to produce potential carcinogens (especially in beryllium workers with short-term employment). Problems in the design and conduct of the studies further weaken the strength of the findings. There appeared to be a tendency on the part of the authors to overemphasize the positive nature of their results and minimize the contribution of qualifying factors. A list of these problems is presented in Table 7-10. If the errors detailed in the preceding paragraphs were corrected and proper consideration given to addressing the problems described above, the finding of a significant excess risk would probably no longer be apparent, although the possibility nevertheless remains that a portion of the reported excess lung cancer risk may in fact be due to beryllium exposure. Thus, the Carcinogen Assessment Group (CAG) feels that the findings of these studies must be considered to be at least suggestive. The International Agency for Research on Cancer (IARC) has concluded that beryllium and its compounds should be classified as "limited" with respect to

TABLE 7-9. COMPARISON OF STUDY COHORTS AND SUBCOHORTS OF TWO BERYLLIUM COMPANIES

	Company where employed[a]	Source	Period of employment	Comparison population	Termination date of follow-up	Chief lung cancer results[b]
Bayliss et al. (1971)	KBI, BRUSH 6,818 males	Personnel records	1942-1967	U.S. males	1967	Total 36 (O), 34.1 (E)
Bayliss and Lainhart (1972)	KBI only 3,795 white males	Same as above	1942-1967	U.S. white males	1967	Total 25 (O), 23 (E) Latency 15 yrs + 14 (O), 13.3 (E)
Bayliss and Wagoner (1977)	KBI-Reading Facility only 3,070 white males	Same as above	1942-1967	U.S. white males	1975	Total 46 (O), 33 (E) ($P < 0.05$) Latency 15 yrs + 37 (O), 24 (E) ($P < 0.05$)
Wagoner et al. (1980)	KBI-Reading Facility only 3,055 white males	Same as above	1942-1967	U.S. white males	1975	Total 47 (O), 34.3 (E) ($P < 0.05$) Latency 15 yrs + 20 (O), 10.8 (E) ($P < 0.05$)
Mancuso and El-Attar (1969)	KBI, BRUSH 3,685 white males	Social Security Quarterly Earnings Reports	1937-1948	Industrial Control (Unidentified)	1966	Equivocal

(continued on the following page)

TABLE 7-9. (continued)

	Company where employed[a]	Source	Period of employment	Comparison population	Termination date of follow-up	Chief lung cancer results[b]
Mancuso (1970)	KBI, BRUSH 3,685 white males	Social Security Quarterly Earnings Reports	1937-1944 and 1945-1948	Internal Control	1966	Duration of employment (rate) ≥ 1 1/4 yrs 33.2/10^5 ≤ 1 1/4 yrs 99.9/10^5 Prior respiratory disease only with 284.3/10^5 without 77.7/10^5
Mancuso (1979)	KBI-2044 BRUSH-1,222 white males	Same	1942-1948	U.S. white males	BRUSH 1974 KBI 1975	Latency 15 yrs + only Ohio - 22 (O), 9.9 (E) ($P < 0.01$) Pennsylvania - 36 (O), 22 (E) ($P < 0.01$) Mobility (deaths) Among departments 80 (O), 57.1 (E) ($P < 0.01$)
Mancuso (1980)	KBI 3,685 white males	Same	1937-1948	Viscous rayon workers	1976	Remained in same department 80 (O), 50.6 (E) ($P < 0.01$)

[a] KBI = Kawecki-Berylco Industries (Pennsylvania).

BRUSH = Brush Beryllium Co. (Ohio).

[b] (O) = observed

(E) = expected

TABLE 7-10. PROBLEMS WITH BERYLLIUM COHORT STUDIES

Bayliss et al. (1971)	A.	Loss of 2,000 individuals because of insufficient data.
	B.	No latency considerations.
	C.	Combined study populations of several plants from 2 companies.
Bayliss and Lainhart (1972)	A.	Includes clerical and administrative personnel with no exposure.
	B.	No independent assessment plant employment files.
	C.	Latency after 20 years not assessed.
Bayliss and Wagoner (1977) and Wagoner et al. (1980)	A.	Cigarette smoking a possible confounder.
	B.	Overestimate of lung cancer deaths in comparison population by 11 percent.
	C.	Inclusion of 1 lung cancer victim who did not fit definition for inclusion.
	D.	Loss of 295 individuals from study cohort.
	E.	Exposure to potential carcinogens prior and post beryllium employment.
Mancuso and El-Attar (1969)	A.	Unidentified comparison population.
	B.	Internal rates based upon small numbers.
	C.	Tremendous variability and impossible to test significance.
	D.	No smoking consideration as possible confounder.
Mancuso (1970)	A.	Internal rates based upon small numbers.
	B.	Inappropriate comparison (age group 15-24 left out of comparison).
	C.	No consideration of smoking as a possible confounder.
	D.	No consideration of latency.
	E.	Exposure to potential carcinogens prior and post beryllium employment.
Mancuso (1979)	A.	Overestimate of lung cancer deaths in comparison population by 11 percent.
	B.	No consideration of smoking as a possible confounder.
	C.	Incomplete delineation of cohort from use of Social Security Quarterly Earnings reports.
	D.	Exposure to potential carcinogens prior and post beryllium employment.
Mancuso (1980)	A.	No consideration of latent effects.
	B.	Probable lack of age adjustment.
	C.	No consideration of effects of smoking.
	D.	No description of origin or makeup of comparison cohort except for age.
	E.	Overestimate of lung cancer deaths in comparison population by 11 percent.

the human epidemiologic evidence of carcinogenicity. The CAG regards the epidemiologic evidence of beryllium carcinogenicity in beryllium-exposed workers as limited to inadequate.

7.3 QUANTITATIVE ESTIMATION

This quantitative section deals with estimation of the unit risk for beryllium as a potential carcinogen in air, and compares the potency of beryllium to other carcinogens that have been evaluated by the CAG. The unit risk for an air pollutant is defined as the incremental lifetime cancer risk to humans from daily exposure to a concentration of 1 $\mu g/m^3$ of the pollutant in air by inhalation.

The unit risk estimate for beryllium represents an extrapolation below the dose range of experimental data. There is currently no solid scientific basis for any mathematical extrapolation model that relates exposure to cancer risk at the extremely low concentrations, including the unit concentration given above, that must be dealt with in evaluating environmental hazards. For practical reasons, the correspondingly low levels of risk cannot be measured directly either by animal experiments or by epidemiologic study. Low-dose extrapolation must, therefore, be based on current understanding of the mechanisms of carcinogenesis. At the present time, the dominant view of the carcinogenic process involves the concept that most cancer-causing agents also cause irreversible damage to DNA. This position is based in part on the fact that a very large proportion of agents that cause cancer are also mutagenic. There is reason to expect that the quantal response that is characteristic of mutagenesis is associated with a linear (at low doses) nonthreshold dose-response relationship. Indeed, there is substantial evidence from mutagenicity studies with both ionizing radiation and a wide variety of chemicals that this type of dose-response model is the appropriate one to use. This is particularly true at the lower end of the dose-response curve; at high doses, there can be an upward curvature, probably reflecting the effects of multistage processes on the mutagenic response. The linear (at low doses) nonthreshold dose-response relationship is also consistent with the relatively few epidemiologic studies of cancer responses to specific agents that contain enough information to make the evaluation possible (e.g., radiation-induced leukemia, breast and thyroid cancer, skin cancer induced by arsenic in drinking water, liver cancer induced by aflatoxins in the diet). Some supporting evidence also exists from animal experiments (e.g., the initiation stage of the two-stage carcinogenesis model in rat liver and mouse skin).

Because its scientific basis, although limited, is the best of any of the current mathematical extrapolation models, the nonthreshold model, which is linear at low doses, has been adopted as the primary basis for risk extrapolation to low levels of the dose-response relationship. The risk estimates made with such a model should be regarded as conservative, representing a plausible upper limit for the risk: i.e., the true risk is not likely to be higher than the estimate, but it could be lower.

For several reasons, the unit risk estimate based on animal bioassays is only an approximate indication of the absolute risk in populations exposed to known carcinogen concentrations. First, there are important species differences in uptake, metabolism, and organ distribution and elimination of carcinogens, as well as species differences in target site susceptibility, immunological responses, hormone function, dietary factors, and disease. Second, the concept of equivalent doses for humans as compared to animals on a mg/surface area basis is virtually without experimental verification as regards carcinogenic response. Finally, human populations are variable with respect to genetic constitution and diet, living environment, activity patterns, and other cultural factors.

The unit risk estimate can give a rough indication of the relative potency of a given agent as compared with other carcinogens. Such estimates are, of course, more reliable when the comparisons are based on studies in which the test species, strain, sex, and routes of exposure are similar.

The quantitative aspect of carcinogen risk assessment is addressed here because of its possible value in the regulatory decision-making process, e.g., in setting regulatory priorities, evaluating the adequacy of technology-based controls, etc. However, the imprecision of presently available technology for estimating cancer risks to humans at low levels of exposure should be recognized. At best, the linear extrapolation model used here provides a rough but plausible estimate of the upper limit of risk--that is, with this model it is not likely that true risk would be much more than the estimated risk, but it could be considerably lower. The risk estimates presented in subsequent sections should not be regarded, therefore, as accurate representations of the true cancer risks even when the exposures involved are accurately defined.

The estimates presented may, however, be factored into regulatory decisions to the extent that the concept of upper-risk limits is found to be useful.

7.3.1 Procedures for the Determination of Unit Risk

7.3.1.1 Low-Dose Extrapolation Model--Two dose-response models, which are derivatives of the theory of multistage carcinogenesis, are used to calculate the unit risk of beryllium on the basis of animal data. The selection of these two models is dictated by the nature of the data available for quantitative risk assessment. The first model, a multistage model that allows for a time-dependent dose pattern, was developed by Crump and Howe (1984), and uses the theory of multistage carcinogenesis developed by Armitage and Doll (1961). The Armitage-Doll multistage model assumes that a cell is capable of generating a neoplasm when it has undergone k changes in a certain order. The rate, r_i, of the i^{th} change is assumed to be linearly related to D(t), the dose at age t, i.e., $r_i = a_i + b_i D(t)$, where a_i is the background rate, and b_i is the proportionality constant for the dose. It can be shown that the probability of cancer by age t is given by

$$P(t) = 1 - \exp\,[-H(t)]$$

where

$$H(t) = \int_0^t \int_0^{u_k} \cdots \int_0^{u_2} \{[a_1 + b_1 D(u_1)] \ldots [(a_k + b_k D(u_k)]\}\, du_1 \ldots du_k$$

is the cumulative incidence rate by time t.

When H(t) or the risk of cancer is small, P(t) is approximately equal to H(t). When only one stage is dose-related, all proportionality constants are zero except for the proportionality constant for the dose-related stage.

This model will be applied to the data in Reeves and Deitch (1969) where the dose D(t) is constant for t in an interval $[S_1, S_2]$ and is zero elsewhere. Under this particular exposure pattern and the assumption that only a single stage is dose-related, the term H(t) can be written as the sum of two components $H_1(t)$ and $H_2(t)$ where $H_1(t) = a_1 \cdot a_2 \ldots a_k\, t^k/k!$ represents the background cumulative incidence and $H_2(t)$ is the incremental cumulative incidence due to exposure. Three special cases of H_2 which are often used to interpret a given set of data are given below.

$$H_2(t) = \frac{d b_1 (\Pi a_i)}{k!\, a_1} \times \begin{cases} 0 & t < s_1 \\ (t - s_1)^k & s_1 \leq t < s_2 \\ (t - s_1)^k - (t - s_2)^k & s_2 \leq t \end{cases}$$

if the first stage is affected (r = 1),

$$H_2(t) = \frac{d b_{k-1} (\Pi a_i)}{k!\, a_{k-1}} \times \begin{cases} 0 & t < s_1 \\ t^k - s_1^{k-1} [kt - (k - 1) s_1] & s_1 \leq t < s_2 \\ s_2^{k-1} [kt - (k-1) s_2] - s_1^{k-1} [kt - (k-1) s_1] & s_2 \leq t \end{cases}$$

if the penultimate stage is affected (r = k - 1), and

$$H_2(t) = \frac{d b_k (\Pi a_i)}{k!\, a_k} \times \begin{cases} 0 & t < s_1 \\ t^k - s_1^k & s_1 \leq t < s_2 \\ s_2^k - s_1^k & s_2 \leq t \end{cases}$$

if the last stage is affected (r = k).

A computer program, ADOLL1-83, has been developed by Crump and Howe (1984) to implement the computational aspect of the model. In this program, the model is generalized to include tumor induction time I by replacing the time factor t by t-I. The best-fit model is identified as the one that has the maximum likelihood, among various models with different numbers of stages and the stage affected by the exposure.

The second model used to calculate the carcinogenic potency of beryllium is the one-hit model with zero background rate. This model is used because all the experiments, except that of Reeves and Deitch (1969), had only one data point and did not have a control group. The slope, b, of the one-hit model, $P(d) = 1 - \exp(-bxd)$, is calculated by the formula

$$b = [-\mathrm{Ln}(1-P)]/d$$

Since the background rate is zero, the least-square estimate b, as calculated above, is also a maximum-likelihood estimate.

7.3.1.2 Selection of Data--For some chemicals, several studies in different animal species, strains, and sexes, each run at several doses and different routes of exposure, are available. A choice must be made as to which of the data sets from several studies to use in the model. It may also be appropriate to correct for metabolism differences between species and for absorption factors via different routes of administration. The procedures used in evaluating these data are consistent with the approach of making a maximum-likely risk estimate. They are as follows:

1. The tumor incidence data are separated according to organ sites or tumor types. The set of data (i.e., dose and tumor incidence) used in the model is the set where the incidence is statistically significantly higher than the control for at least one test dose level and/or where the tumor incidence rate shows a statistically significant trend with respect to dose level. The data set that gives the highest estimate of the lifetime carcinogenic risk, q_1^*, is selected in most cases. However, efforts are made to exclude data sets that produce spuriously high risk estimates because of a small number of animals. That is, if two sets of data show a similar dose-response relationship, and one has a very small sample size, the set of data having the larger sample size is selected for calculating the carcinogenic potency.

2. If there are two or more data sets of comparable size that are identical with respect to species, strain, sex, and tumor sites, the geometric mean of q_1^*, estimated from each of these data sets, is used for risk assessment. The geometric mean of numbers A_1, A_2, ..., A, is defined as

$$(A_1 \times A_2 \times \ldots \times A_m)^{1/m}$$

3. If two or more significant tumor sites are observed in the same study, and if the data are available, the number of animals with at least one of the specific tumor sites under consideration is used as incidence data in the model.

7.3.1.3 Calculation of Human Equivalent Dosages--Following the suggestion of Mantel and Schneiderman (1975), it is assumed that mg/surface area/day is an equivalent dose between species. Since, to a close approximation, the surface area is proportional to the two-thirds power of the weight, as would be the case for a perfect sphere, the exposure in mg/day per two-thirds power of the weight is also considered to be equivalent exposure. In an animal experiment, this equivalent dose is computed in the following manner.

Let

L_e = duration of experiment

l_e = duration of exposure

m = average dose per day in mg during administration of the agent (i.e., during l_e), and

W = average weight of the experimental animal.

Then, the lifetime exposure is

$$d = \frac{l_e \times m}{L_e \times W^{2/3}}$$

7.3.1.3.1 Oral Exposure. Often exposures are not given in units of mg/day, and it becomes necessary to convert the given exposures into mg/day. Similarly, in drinking water studies, exposure is expressed as ppm in the water. For example, in most feeding studies exposure is given in terms of ppm in the diet. In these cases, the exposure in mg/day is

$$m = \text{ppm} \times F \times r$$

where ppm is parts per million of the carcinogenic agent in the diet or water, F is the weight of the food or water consumed per day in kg, and r is the absorption fraction. In the absence of any data to the contrary, r is assumed to be equal to one. For a uniform diet, the weight of the food consumed is proportional to the calories required, which in turn is proportional to the surface area, or two-thirds power of the weight. Water demands are also assumed to be proportional to the surface area, so that

$$m \propto ppm \times W^{2/3} \times r$$

or

$$\frac{m}{rW^{2/3}} \propto ppm$$

As a result, ppm in the diet or water is often assumed to be an equivalent exposure between species. However, this may not be justified for the present study, since the ratio of calories to food weight is very different in the diet of man as compared to laboratory animals, primarily due to differences in the moisture content of the foods eaten. For the same reason, the amount of drinking water required by each species also differs. It therefore would be necessary to use an empirically-derived factor, f = F/W, which is the fraction of an organism's body weight that is consumed per day as food, expressed as follows:

		Fraction of body weight consumed as	
Species	W	f_{food}	f_{water}
Man	70	0.028	0.029
Rats	0.35	0.05	0.078
Mice	0.03	0.13	0.17

Thus, when the exposure is given as a certain dietary or water concentration in ppm, the exposure in mg/$W^{2/3}$ is

$$\frac{m}{rW^{2/3}} \propto \frac{ppm \times F}{W^{2/3}} = \frac{ppm \times f \times W}{W^{2/3}} = ppm \times f \times W^{1/3}$$

When exposure is given in terms of mg/kg/day = m/Wr = s, the conversion is simply

$$\frac{m}{rW^{2/3}} \propto s \times W^{1/3}$$

7.3.1.3.2 Inhalation Exposure. When exposure is via inhalation, the calculation of dose can be considered for two cases where 1) the carcinogenic agent is either a completely water-soluble gas or an aerosol and is absorbed proportionally to the amount of air breathed in, and 2) where the carcinogen is a poorly water-soluble gas which reaches an equilibrium between the air breathed and the body compartments. After equilibrium is reached, the rate of absorption of these agents is expected to be proportional to the metabolic rate, which is proportional to the rate of oxygen consumption, which in turn is a function of surface area.

7.3.1.3.2.1 Case 1. Agents that are in the form of particulate matter or virtually completely absorbed gases, such as sulfur dioxide, can reasonably be expected to be absorbed proportionally to the breathing rate. In this case the exposure in mg/day may be expressed as

$$m = I \times v \times r$$

where I = inhalation rate per day in m^3, v = mg/m^3 of the agent in air, and r = the absorption fraction.

The inhalation rates, I, for various species can be calculated from the observations of the Federation of American Societies for Experimental Biology (FASEB, 1974) that 25-g mice breathe 34.5 liters/day and 113-g rats breathe 105 liters/day. For mice and rats of other weights, W (in kilograms), the surface area proportionality can be used to find breathing rates in m^3/day as follows:

$$\text{For mice, } I = 0.0345\ (W/0.025)^{2/3}\ m^3/\text{day}$$

$$\text{For rats, } I = 0.105\ (W/0.113)^{2/3}\ m^3/\text{day}$$

For humans, the value of 20 m^3/day* is adopted as a standard breathing rate (International Commission on Radiological Protection, 1977). The equivalent exposure in $mg/W^{2/3}$ for these agents can be derived from the air intake data in a way analogous to the food intake data. The empirical factors for the air intake per kg per day, $i = I/W$, based upon the previously stated relationships, are tabulated as follows:

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*From "Recommendation of the International Commission on Radiological Protection," page 9. The average breathing rate is 10^7 cm^3 per 8-hour workday and 2×10^7 cm^3 in 24 hours.

Species	W	i = I/W
Man	70	0.29
Rats	0.35	0.64
Mice	0.03	1.3

Therefore, for particulates or completely absorbed gases, the equivalent exposure in $mg/W^{2/3}$ is

$$d = \frac{m}{W^{2/3}} = \frac{Ivr}{W^{2/3}} = \frac{iWvr}{W^{2/3}} = iW^{1/3}vr$$

In the absence of experimental information or a sound theoretical argument to the contrary, the fraction absorbed, r, is assumed to be the same for all species.

7.3.1.3.2.2 Case 2. The dose in mg/day of partially soluble vapors is proportional to the O_2 consumption, which in turn is proportional to $W^{2/3}$ and to the solubility of the gas in body fluids, which can be expressed as an absorption coefficient, r, for the gas. Therefore, expressing the O_2 consumption as $O_2 = k\,W^{2/3}$, where k is a constant independent of species, it follows that

$$m = k\,W^{2/3} \times v \times r$$

or

$$d = \frac{m}{W^{2/3}} = kvr$$

As with Case 1, in the absence of experimental information or a sound theoretical argument to the contrary, the absorption fraction, r, is assumed to be the same for all species. Therefore, for these substances a certain concentration in ppm or $\mu g/m^3$ in experimental animals is equivalent to the same concentration in humans. This is supported by the observation that the minimum alveolar concentration necessary to produce a given "stage" of anesthesia is similar in man and animals (Dripps et al., 1977). When the animals are exposed via the oral route and human exposure is via inhalation or vice versa, the assumption is made, unless there is pharmacokinetic evidence to the contrary, that absorption is equal by either exposure route.

7.3.1.4 Calculation of the Unit Risk from Animal Studies--The risk associated with d mg/kg$^{2/3}$/day is obtained from GLOBAL79, and for most cases of interest to risk assessment, can be adequately approximated by $P(d) = 1 - \exp(-q_1^* d)$. A "unit risk" in units X is simply the risk corresponding to an exposure of X = 1. This value is estimated by finding the number of mg/kg$^{2/3}$/day that corresponds to one unit of X, and substituting this value into the above relationship. Thus, for example, if X is in units of μg/m^3 in the air, then for case 1, $d = 0.29 \times 70^{1/3} \times 10^{-3}$ mg/kg$^{2/3}$/day, and for case 2, d = 1, when μg/m^3 is the unit used to compute parameters in animal experiments.

If exposures are given in terms of ppm in air, the following calculation may be used:

$$1 \text{ ppm} = 1.2 \times \frac{\text{molecular weight (gas)}}{\text{molecular weight (air)}} \text{ mg/m}^3$$

Note that an equivalent method of calculating unit risk would be to use mg/kg for the animal exposures, and then to increase the jth polynomial coefficient by an amount

$$(W_h/W_a)^{j/3} \quad j = 1, 2, \ldots, k,$$

and to use mg/kg equivalents for the unit risk values.

7.3.1.4.1 Adjustments for Less Than Lifespan Duration of Experiment. If the duration of experiment L_e is less than the natural lifespan of the test animal L, the slope q_1^*, or more generally the exponent g(d), is increased by multiplying by a factor $(L/L_e)^3$. We assume that if the average dose d is continued, the age-specific rate of cancer will continue to increase as a constant function of the background rate. The age-specific rates for humans increase at least by the second power of the age and often by a considerably higher power, as demonstrated by Doll (1971). Thus, it is expected that the cumulative tumor rate would increase by at least the third power of age. Using this fact, it is assumed that the slope q_1^*, or more generally the exponent g(d), would also increase by at least the third power of age. As a result, if the slope q_1^* [or g(d)] is calculated at age L_e, it is expected that if the experiment had been continued for the full lifespan L at the given average exposure, the slope q_1^* [or g(d)] would have been increased by at least $(L/L_e)^3$.

This adjustment is conceptually consistent with the proportional hazard model proposed by Cox (1972) and the time-to-tumor model considered by Daffer et al. (1980), where the probability of cancer by age t and at dose d is given by

$$P(d,t) = 1 - \exp\,[-f(t) \times g(d)]$$

7.3.1.5 Model for Estimation of Unit Risk Based on Human Data--If human epidemiologic studies and sufficiently valid exposure information are available for the compound, they are always used in some way. If they show a carcinogenic effect, the data are analyzed to give an estimate of the linear dependence of cancer rates on lifetime average dose, which is equivalent to the factor B_H. If they show no carcinogenic effect when positive animal evidence is available, then it is assumed that a risk does exist, but it is smaller than could have been observed in the epidemiologic study, and an upper limit to the cancer incidence is calculated assuming hypothetically that the true incidence is below the level of detection in the cohort studied, which is determined largely by the cohort size. Whenever possible, human data are used in preference to animal bioassay data.

Very little information exists that can be utilized to extrapolate from high-exposure occupational studies to exposures at low environmental levels. However, if a number of simplifying assumptions are made, it is possible to construct a crude dose-response model whose parameters can be estimated using vital statistics, epidemiologic studies, and estimates of worker exposures.

In human studies, the response is measured in terms of the relative risk of the exposed cohort of individuals as compared with the control group. The mathematical model employed for low-dose extrapolation assumes that for low exposures the lifetime probability of death from cancer, P_0, may be represented by the linear equation

$$P_0 = A + B_H x$$

where A is the lifetime probability in the absence of the agent, and x is the average lifetime exposure to environmental levels in units such as ppm. The factor B_H is the increased probability of cancer associated with each unit increase of x, the agent in air.

If it is assumed that R, the relative risk of cancer for exposed workers as compared to the general population, is independent of length of exposure or age at exposure, and depends only upon average lifetime exposure, it follows that

$$R = \frac{P}{P_0} = \frac{A + B_H (x_1 + x_2)}{A + B_H x_1}$$

or

$$RP_0 = A + B_H (x_1 + x_2)$$

where x_1 = lifetime average daily exposure to the agent for the general population, x_2 = lifetime average daily exposure to the agent in the occupational setting, and P_0 = lifetime probability of dying of cancer with no or negligible exposure.

Substituting $P_0 = A + B_H (x_1)$ and rearranging gives

$$B_H = P_0 (R - 1)/x_2$$

To use this model, estimates of R and x_2 must be obtained from epidemiologic studies. The value P_0 is derived by means of the life table methodology from the age- and cause-specific death rates for the general population found in U.S. vital statistics tables.

7.3.2 Estimation of the Carcinogenic Risk of Beryllium

7.3.2.1 Calculation of the Carcinogenic Potency of Beryllium on the Basis of Animal Data--Only the data from inhalation studies are used for risk assessment because the route of administration is an exposure route of interest to humans. Although there are many animal studies showing carcinogenic effects of beryllium by inhalation, the data that can be used for estimating the carcinogenic risks associated with beryllium are very limited. Except for Reeves and Deitch (1969), most of the studies were not well documented, were conducted at single dose levels, and did not include control groups. In Reeves and Deitch (1969), animals were exposed to nine different dose patterns, varying in the duration of exposure and the time at which exposure was begun and terminated. The data from Reeves and Deitch (1969) and seven other studies that had only single dose levels are used herein to calculate the carcinogenic potency of beryllium. For the Reeves and Deitch data, the multistage model with time-dependent dose patterns is used as the low-dose extrapolation model. The data and the calculations are presented in Appendix A. For the studies with single dose levels, the one-hit model, as described in Section 7.3.1.1, is used as the low-dose extrapolation model. The data for the seven studies with single dose levels, and potency estimates on the basis of all eight of the data sets, are presented in Table 7-11.

In all of these calculations, the equivalent dose d is arrived at by using the procedure described as Case 1 in Section 7.3.1.3.2.1. This procedure is illustrated as follows: For 1 $\mu g/m^3$ of beryllium in air, the total beryllium intake for a rat weighing 0.35 kg is $I_A = 1\ \mu g/m^3 \times 0.224\ m^3/day = 0.224$ $\mu g/day$, where 0.224 m^3/day is assumed to be the volumetric breathing rate for a rat weighing 0.35 kg. Assuming that doses are equivalent among species on the basis of surface area, the human equivalent dose C ($\mu g/m^3$) satisfies the equation

$$(20\ m^3/day) \times C\ (\mu g/m^3)/(70)^{2/3} = 0.224/(0.35)^{2/3}$$

or $C = 0.38\ \mu g/m^3$, where 20 m^3/day is assumed to be the volumetric breathing rate for a 70-kg human. Therefore, the human equivalent dose in $\mu g/m^3$ is obtained by multiplying the experimental dose by 0.38. The last column of Table 7-11 presents the carcinogenic potency of beryllium as calculated from each of the eight inhalation studies. The potency level ranges from $2.9 \times 10^{-3}/(\mu g/m^3)$ to $4.4/(\mu g/m^3)$. The magnitude of the potency appears to depend upon the form of beryllium used in the experiment. Beryl ore is the least potent compound among the four compounds studied, while beryllium sulfate ($BeSO_4$) is the most potent. Four of the five studies on beryllium sulfate ($BeSO_4$) have potency estimates that approximate $0.5/(\mu g/m^3)$.

7.3.2.2 Calculation of the Carcinogenic Potency of Beryllium on the Basis of Human Data--Given the need to estimate the cancer risk of beryllium and the uncertainty inherent in the use of animal data, it is desirable to use the

TABLE 7-11. BERYLLIUM DOSE-RESPONSE DATA FROM SEVEN INHALATION STUDIES ON RATS, AND THE CORRESPONDING POTENCY (SLOPE) ESTIMATIONS

Investigator	Beryllium compound	Mean beryllium concentration ($\mu g/m^3$) exposure pattern	Standardized experimental dose ($\mu g/m^3$)[a]	Pulmonary tumor incidence rate	Human equivalent dose (μg Be/m^3)	Maximum likelihood estimate slope[b] $(\mu g/m^3)^{-1}$
Vorwald (1953)	$BeSO_4$	33 μg Be/m^3 35 hours/week for 13 months	5.0	4/8	1.9	0.36
Schepers (1957)	$BeSO_4$	33.5 μg Be/m^3 35 hours/week for 7.5 months	2.9	58/136	1.1	0.51
Schepers (1961)	$BeHPO_4$	227 μg Be/m^3 35 hours/week for 6.5 months	17.1	7/40	6.5	3.0×10^{-2}
Schepers (1961)	BeF_2	9 μg Be/m^3 35 hours/week for 10.5 months	1.1	11/200	0.42	0.13
Vorwald et al. (1966)	$BeSO_4$	2.8 μg Be/m^3 35 hours/week for 18 months	0.58	13/21	0.22	4.4
Reeves and Deitch (1969)	$BeSO_4$	35.7 μg Be/m^3 35 hours/week for 18 months	7.4	13/15	2.8	0.72
Wagner et al. (1969)	beryl ore	620 μg Be/m^3 intermittantly for 17 months	585.6	9/19	222.5	2.9×10^{-3}
Reeves and Deitch (1969)	$BeSO_4$	See Appendix A for details				0.81

[a] Standardized experimental dose is calculated by d x (h/168) x (L/18) where d is the mean experimental concentration, h is the number of hours exposed per week (168 hours), and L is the number of months exposed.

[b] Estimated by assuming that the control response is zero.

Source: Reeves, 1978.

available human data in some way to estimate the carcinogenic potency of beryllium. Data from Mancuso (1979) and a sub-cohort from Wagoner et al. (1980) are considered appropriate for this purpose. The reason these two studies were selected is that their cohorts consisted of beryllium workers employed prior to 1949, when controls on beryllium in the workplace began. The workers' exposures to beryllium before 1949 were very high. A 1947 study reviewed by NIOSH (1972) reported beryllium concentrations in a beryllium extraction plant in Pennsylvania of up to 8,840 $\mu g/m^3$. In more than 50 percent of the determinations reviewed, beryllium concentrations were in excess of 100 $\mu g/m^3$. According to NIOSH (1972), the levels of environmental exposure to beryllium in the workplace were markedly reduced after control measures were instituted in 1949. In one Ohio extraction plant, the beryllium exposure levels were recorded at 2 $\mu g/m^3$ or less during almost all of a 7-year period. We summarize below the information available about beryllium exposure levels in the workplace and the excess cancer risk observed among workers employed in beryllium production plants.

7.3.2.2.1 Information on Exposure Levels. The beryllium production plants studied by Mancuso (1979) and Wagoner et al. (1980) were major beryllium production plants in Pennsylvania and Ohio. The workplace concentrations of beryllium in these plants were found to be comparable (Eisenbud, 1983). Based on the NIOSH (1972) report described previously, the lower-bound estimate of the median exposure concentration exceeded 100 $\mu g/m^3$ since more than 50 percent of the determinations exceeded that level. To sharpen the estimate, if we assume that the logarithmic transformation of the concentration follows log-normal distribution and that the values of 100 and 8,840 $\mu g/m^3$ correspond, respectively, to the 45th and the 95th percentiles of the determinations, then the median value would approximately equal 160 $\mu g/m^3$. According to Eisenbud and Lisson (1983), it is likely this value is an underestimation of the actual median exposure level in the workplace, and thus should be considered to be a lower-bound estimate of the median level. Eisenbud and Lisson (1983) stated "...published studies of conditions in the Pennsylvania production plant indicate that the levels of exposure prior to installation of dust controls were comparable to conditions in the Ohio plants. Concentrations in excess of 1,000 $\mu g/m^3$ were commonly found in all three extraction plants during the late 1940's." On the other hand, it is unlikely that the median level could greatly exceed 1,000 $\mu g/m^3$, since at that level almost all of the exposed workers developed acute respiratory diseases (Eisenbud, 1955). Thus, it is reasonable to assume that the median level of beryllium concentration did not exceed 1,000 $\mu g/m^3$. In the risk calculation, the median level of beryllium concentration is assumed to range from 160 $\mu g/m^3$ to 1,000 $\mu g/m^3$. This is the narrowest range for median exposure that we could obtain on the basis of available information.

7.3.2.2.2 Information on Excess Risk.

7.3.2.2.2.1 Mancuso (1979). In this study, cohorts of beryllium-exposed workers employed in two major beryllium production plants, one in Ohio (1,222 workers) and another in Pennsylvania (2,044 workers), during 1942-1948, were identified from records of the Social Security Administration. Follow-ups were performed through 1974 for the Ohio cohort and through 1975 for the Pennsylvania cohort. The worker turnover rates in these cohorts were very high. For most of the workers, the duration of employment was less than 5 years. It is possible that the workers for whom duration of employment was less than 5 years were exposed to higher concentrations of beryllium than those for whom duration of employment was longer than 5 years. Since the installation of the control measures in 1949 had significantly reduced beryllium concentrations in the plant, a longer duration of employment does not necessarily imply a greater total cumulative exposure. Table 7-12 presents the observed and expected lung cancer deaths among white male workers who were employed at least 15 years ago at the end of follow-up. The duration of employment did not appear to correlate with the lung cancer mortality rate, a finding that could be explained in several ways. One possible explanation is that the workers with shorter duration of employment may have been exposed to higher concentrations of beryllium than the workers with longer duration of employment. The Working Group on Beryllium (IARC, 1980) observed that short exposure to beryllium was also correlated to the "chemical respiratory illness" which occurred only when exposure exceeded a certain level of concentration (Eisenbud, 1955).

7.3.2.2.2.2 Wagoner et al. (1980). Wagoner et al. (1980) conducted a cohort study of 3,055 white males who were initially employed in a plant in Pennsylvania during 1942 to 1967, and who were followed to December 30, 1975. Of particular interest to the present risk assessment is a subcohort of workers who were initially employed prior to 1950 and who were followed for at least 15 years from the date of initial employment. A significant elevation of lung

TABLE 7-12. OBSERVED/EXPECTED LUNG CANCER DEATHS (RELATIVE RISK) AMONG WHITE MALE WORKERS WHO WERE EMPLOYED AT LEAST 15 YEARS AGO AT THE END OF FOLLOW-UP

Plant	Duration of employment (years)			
	<1	1-4	>5	Total
Ohio	14/6.48 (2.16)	5/1.74 (2.87)	3/1.63 (1.84)	22/9.86 (2.23)
Pennsylvania	23/12.84 (1.79)	10/5.27 (1.90)	3/3.91 (0.77)	36/20.02 (1.67)

Source: Mancuso, 1979.

cancer risk (24 observed vs. 13.42 expected, or a relative risk of 1.79) was observed in this subcohort.

Although there is great uncertainty about the adequacy of the epidemiologic studies considered herein, the use of a particular relative risk estimate in the risk calculation should not be affected because all of the relative risk estimates have values of approximately 2. Even if all of the studies were negative, a statistical upper-bound estimate of a relative risk would be approximately equal to the reported value. Thus, the adequacy of the studies would affect only the conclusion as to whether or not beryllium is carcinogenic to humans and is not of great relevance to the risk estimation. A major uncertainty of the risk estimate for beryllium comes from the derivation of exposure level in the workplace and the temporal effect of the patterns of exposure. To account for these uncertainties, the "effective" exposure level of concentration is calculated in several ways.

To calculate the lifetime cancer risk on the basis of information described previously, the median level of beryllium exposure must be converted to the "effective" dose through multiplying by a factor of $(8/24) \times (240/365) \times (f/L)$ to reflect that workers were exposed to beryllium 8 hours/day, 240 days/year for f years out of a period of L years at risk (i.e., from the onset of employment to the termination of follow-up). Two values of f/L are used in the calculation: $f/L = 1$ and $f/L = 0.25$. The use of $f/L = 1$ would avoid overestimating the risk (but could underestimate the risk) if the observation by Reeves and Deitch (1969) that tumor yield depends not on length of exposure but on how early in life the exposure occurs. Table 7-13 presents a range of

TABLE 7-13. CANCER POTENCY ESTIMATES CALCULATED UNDER VARIOUS ASSUMPTIONS

Beryllium concentration in workplace ($\mu g/m^3$)	f/L	"Effective" dose ($\mu g/m^3$)[a]	Relative risk	Cancer potency[b] $(\mu g/m^3)^{-1}$
160	1	35.07	2.23	1.26×10^{-3}
			1.67	6.88×10^{-4}
			1.79	8.11×10^{-4}
	0.25	8.77	2.23	5.04×10^{-3}
			1.67	2.75×10^{-3}
			1.79	3.24×10^{-3}
1,000	1	219.18	2.23	2.02×10^{-4}
			1.67	1.10×10^{-4}
			1.79	1.30×10^{-4}
	0.25	54.79	2.23	8.08×10^{-4}
			1.67	4.40×10^{-4}
			1.79	5.19×10^{-4}

[a] "Effective dose" is calculated by multiplying the beryllium concentration in workplace by the factor (8/24) x (240/365) x (f/L).

[b] For a given "effective" dose d and a relative risk R, the carcinogenic potency is calculated by the formula $B = (R-1) \times 0.036/d$ where 0.036 is the estimated lung cancer mortality rate in the U.S. population.

cancer potency estimates calculated under various assumptions about relative risk estimates and levels of exposure. The potency estimates range from $1.10 \times 10^{-4}/(\mu g/m^3)$ to $5.04 \times 10^{-3}/(\mu g/m^3)$.

7.3.2.3 Risk Due to Exposure to 1 $\mu g/m^3$ of Beryllium in Air--Except for the study on beryl ore (Wagner et al., 1969), all of the animal studies evaluated in the present report produce considerably higher potency estimates than those calculated on the basis of human data. A possible explanation is that a specific beryllium compound (e.g., $BeSO_4$) was used in animal experiments, whereas workers were exposed to a combination of several forms of compounds. If one adopts the most conservative approach, the upper-bound potency estimate $4.4/(\mu g/m^3)$ would be used to represent the carcinogenic potential of beryllium. This potency is estimated on the basis of data observed in an experiment in which the level of exposure was very similar to the occupational exposure. Thus, the high potency estimate is not simply due to the use of a particular extrapolation model. The use of such a potency estimate would overestimate the human risk and is not consistent with the human experience in the beryllium industry. Therefore, the CAG recommends that the estimate of $7.4 \times 10^{-4}/(\mu g/m^3)$ be used as the carcinogenic potency of beryllium. This value is the geometric mean of 12 potency estimates calculated on the basis of human data under various assumptions. On this basis, the incremental risk associated with 1 $\mu g/m^3$ of beryllium in air is estimated to be 7.4×10^{-4}. This estimate could be considered to be an upper-bound estimate of the cancer risk because low-dose linearity is assumed in the extrapolation.

7.3.3 Comparison of Potency With Other Compounds

One of the uses of quantitative potency estimates is to compare the relative potencies of carcinogens. Figure 7-2 is a histogram representing the frequency distribution of potency indices for 53 suspect carcinogens evaluated by the CAG. The actual data summarized by the histogram are presented in Table 7-14. The potency index used herein was derived from the carcinogenic potency of the compound and is expressed in terms of $(mMol/kg/day)^{-1}$. Where no human data were available, animal oral studies were used in preference to animal inhalation studies, since oral studies have constituted the majority of animal studies.

To calculate the potency index, it is necessary to convert the potency estimate $7.4 \times 10^{-4}/(\mu g/m^3)$ into 2.6/(mg/kg/day), a potency estimate in a different dose unit. The new potency estimate, 2.6/(mg/kg/day), is obtained by dividing $7.4 \times 10^{-4}/(\mu g/m^3)$ by a factor of $(1\ \mu g/m^3) \times (20\ m^3/day)/70\ kg = 2.86 \times 10^{-4}$ mg/kg/day, under the assumption that the volumetric air intake for a 70-kg person is 20 m^3/day. The potency index for beryllium is $2 \times 10^{+1}$, calculated by multiplying the potency estimate, 2.6/mg/kg/day, and the molecular weight of beryllium 9. This calculation places the relative potency of beryllium in the lower part of the third quartile of the 53 suspect carcinogens evaluated by the CAG.

The ranking of relative potency indices is subject to the uncertainties involved in comparing a number of potency estimates for different chemicals based on varying routes of exposure in different species, by means of data from studies whose quality varies widely. All of the indices presented are based on estimates of low-dose risk, using linear extrapolation from the observational range. These indices may not be appropriate for the comparison of potencies if linearity does not exist at the low-dose range, or if comparison is to be made at the high-dose range. If the latter is the case, then an index other than the one calculated above may be more appropriate.

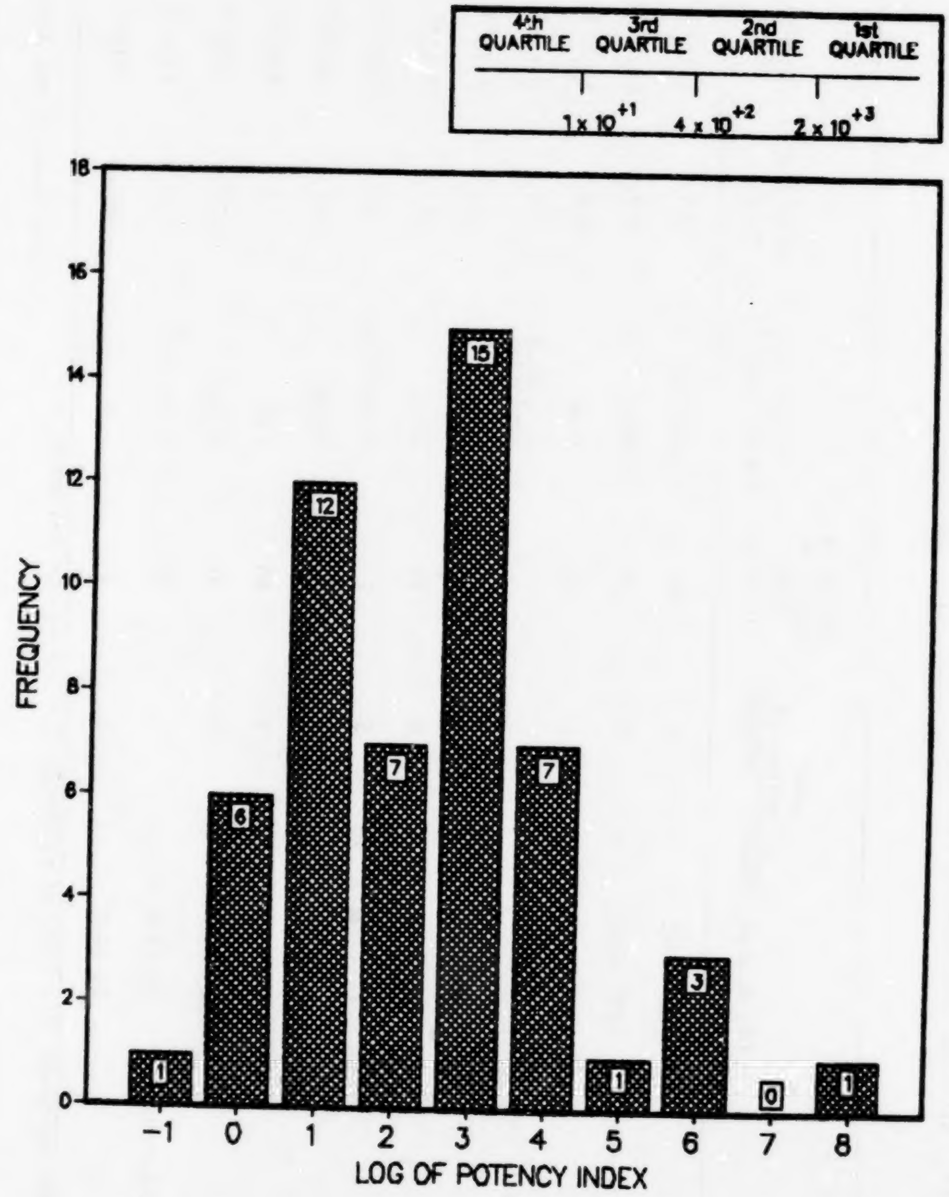

Figure 7-2. Histogram representing the frequency distribution of the potency indices of 53 suspect carcinogens evaluated by the Carcinogen Assessment Group.

TABLE 7-14. RELATIVE CARCINOGENIC POTENCIES AMONG 53 CHEMICALS EVALUATED BY THE CARCINOGEN ASSESSMENT GROUP AS SUSPECT HUMAN CARCINOGENS

Compounds	CAS Number	Level of evidence[a]		Grouping based on IARC criteria	Slope $(mg/kg/day)^{-1}$	Molecular weight	Potency index	Order of magnitude ($\log_{10}$ index)
		Humans	Animals					
Acrylonitrile	107-13-1	L	S	2A	0.24(W)	53.1	$1x10^{+1}$	+1
Aflatoxin B_1	1162-65-8	L	S	2A	2900	312.3	$9x10^{+5}$	+6
Aldrin	309-00-2	I	L	2B	11.4	369.4	$4x10^{+3}$	+4
Allyl chloride					$1.19x10^{-2}$	76.5	$9x10^{-1}$	0
Arsenic	7440-38-2	S	I	1	15(H)	149.8	$2x10^{+3}$	+3
B[a]P	50-32-8	I	S	2B	11.5	252.3	$3x10^{+3}$	+3
Benzene	71-43-2	S	S	1	$5.2x10^{-2}$(W)	78	$4x10^{0}$	+1
Benzidene	92-87-5	S	S	1	234(W)	184.2	$4x10^{+4}$	+5
Beryllium	7440-41-7	L	S	2A	2.6	9	$2x10^{+1}$	+1
Cadmium	7440-43-9	L	S	2A	7.8(W)	112.4	$9x10^{+2}$	+3
Carbon tetrachloride	56-23-5	I	S	2B	$1.30x10^{-1}$	153.8	$2x10^{+1}$	+1
Chlordane	57-74-9	I	L	3	1.61	409.8	$7x10^{+2}$	+3

[a] S = Sufficient evidence; L = Limited evidence; I = Inadequate evidence.

(continued on the following page)

TABLE 7-14. (continued)

Compounds	CAS Number	Level of evidence[a] Humans	Level of evidence[a] Animals	Grouping based on IARC criteria	Slope $(mg/kg/day)^{-1}$	Molecular weight	Potency index	Order of magnitude ($\log_{10}$ index)
Chlorinated ethanes								
1,2-dichloroethane	107-06-2	I	S	2B	6.9×10^{-2}	98.9	7×10^{0}	+1
hexachloroethane	67-72-1	I	L	3	1.42×10^{-2}	236.7	3×10^{0}	0
1,1,2,2-tetrachloroethane	79-34-5	I	L	3	0.20	167.9	$3\times10^{+1}$	+1
1,1,2-trichloroethane	79-00-5	I	L	3	5.73×10^{-2}	133.4	8×10^{0}	+1
Chloroform	67-66-3	I	S	2B	7×10^{-2}	119.4	8×10^{0}	+1
Chromium	7440-47-3	S	S	1	41(W)	100	$4\times10^{+3}$	+4
DDT	50-29-3	I	S	2B	0.34	354.5	$1\times10^{+2}$	+2
Dichlorobenzidine	91-94-1	I	S	2B	1.69	253.1	$4\times10^{+2}$	+3
1,1-dichloroethylene	75-35-4	I	L	3	1.47×10^{-1}(I)	97	$1\times10^{+1}$	+1
Dieldrin	60-57-1	I	S	2B	30.4	380.9	$1\times10^{+4}$	+4
2,4-dinitrotoluene	121-14-2	I	S	2B	0.31	182	$6\times10^{+1}$	+2
Diphenylhydrazine	122-66-7	I	S	2B	0.77	180	$1\times10^{+2}$	+2
Epichlorohydrin	106-89-8	I	S	2B	9.9×10^{-3}	92.5	9×10^{-1}	0
Bis(2-chloroethyl)ether	111-44-4	I	S	2B	1.14	143	$2\times10^{+2}$	+2
Bis(chloromethyl)ether	542-88-1	S	S	1	9300(I)	115	$1\times10^{+6}$	+6

[a] S = Sufficient evidence; L = Limited evidence; I = Inadequate evidence.

(continued on the following page)

TABLE 7-14. (continued)

Compounds	CAS Number	Level of evidence[a] Humans	Level of evidence[a] Animals	Grouping based on IARC criteria	Slope (mg/kg/day)$^{-1}$	Molecular weight	Potency index	Order of magnitude (log$_{10}$ index)
Ethylene dibromide (EDB)	106-93-4	I	S	2B	41	187.9	8x10^{+3}	+4
Ethylene oxide	75-21-8	L	L	2A	1.26(I)	44.1	6x10^{+1}	+2
Heptachlor	76-44-8	I	S	2B	3.37	373.3	1x10^{+3}	+3
Hexachlorobenzene	118-74-1	I	S	2B	1.67	284.4	5x10^{+2}	+3
Hexachlorobutadiene	87-68-3	I	L	3	7.75x10^{-2}	261	2x10^{+1}	+1
Hexachlorocyclohexane								
technical grade					4.75	290.9	1x10^{+3}	+3
alpha isomer	319-84-6	I	S	2B	11.12	290.9	3x10^{+3}	+3
beta isomer	319-85-7	I	L	3	1.84	290.9	5x10^{+2}	+3
gamma isomer	58-89-9	I	L	2B	1.33	290.9	4x10^{+2}	+3
Hexachlorodibenzodioxin	34465-46-8	I	S	2B	6.2x10^{+3}	391	2x10^{+6}	+6
Methylene chloride	75-09-2	I	L	3	6.3x10^{-4}	84.9	5x10^{-2}	-1
Nickel	7440-02-0	L	S	2A	1.15(W)	58.7	7x10^{+1}	+2
Nitrosamines								
Dimethylnitrosamine	62-75-9	I	S	2B	25.9(not by q_1^*)	74.1	2x10^{+3}	+3
Diethylnitrosamine	55-18-5	I	S	2B	43.5(not by q_1^*)	102.1	4x10^{+3}	+4
Dibutylnitrosamine	924-16-3	I	S	2B	5.43	158.2	9x10^{+2}	+3

[a] S = Sufficient evidence; L = Limited evidence; I = Inadequate evidence.

(continued on the following page)

TABLE 7-14. (continued)

Compounds	CAS Number	Level of evidence[a] Humans	Level of evidence[a] Animals	Grouping based on IARC criteria	Slope $(mg/kg/day)^{-1}$	Molecular weight	Potency index	Order of magnitude ($\log_{10}$ index)
N-nitrosopyrrolidine	930-55-2	I	S	2B	2.13	100.2	$2x10^{+2}$	+2
N-nitroso-N-ethylurea	759-73-9	I	S	2B	32.9	117.1	$4x10^{+3}$	+4
N-nitroso-N-methylurea	684-93-5	I	S	2B	302.6	103.1	$3x10^{+4}$	+4
N-nitroso-diphenylamine	86-30-6	I	S	2B	$4.92x10^{-3}$	198	$1x10^{0}$	0
PCBs	1336-36-3	I	S	2B	4.34	324	$1x10^{+3}$	+3
Phenols								
2,4,6-trichlorophenol	88-06-2	I	S	2B	$1.99x10^{-2}$	197.4	$4x10^{0}$	+1
Tetrachlorodibenzo-p-dioxin (TCDD)	1746-01-6	I	S	2B	$1.56x10^{+5}$	322	$5x10^{+7}$	+8
Tetrachloroethylene	127-18-4	I	L	3	$3.5x10^{-2}$	165.8	$6x10^{0}$	+1
Toxaphene	8001-35-2	I	S	2B	1.13	414	$5x10^{+2}$	+3
Trichloroethylene	79-01-6	I	L	3	$1.9x10^{-2}$	131.4	$2.5x10^{0}$	0
Vinyl chloride	75-01-4	S	S	1	$1.75x10^{-2}$(I)	62.5	$1x10^{0}$	0

[a] S = Sufficient evidence; L = Limited evidence; I = Inadequate evidence.

Remarks:

1. Animal slopes are 95% upper-limit slopes based on the linearized multistage model. They are calculated based on animal oral studies, except for those indicated by I (animal inhalation), W (human occupational exposure), and H (human drinking water exposure). Human slopes are point estimates based on the linear nonthreshold model.

2. The potency index is a rounded-off slope in $(mmol/kg/day)^{-1}$ and is calculated by multiplying the slopes in $(mg/kg/day)^{-1}$ by the molecular weight of the compound.

3. Not all of the carcinogenic potencies presented in this table represent the same degree of certainty. All are subject to change as new evidence becomes available.

7.3.4 Summary of Quantitative Assessment

Both animal and human data have been used to calculate the carcinogenic potency of beryllium. Most of the animal studies conducted on beryllium are not well documented, were conducted only at single dose levels, and did not utilize control groups. In the present report, data from eight animal inhalation studies have been used to calculate the upper bounds for the carcinogenic potency of beryllium. The upper-bound potency estimates calculated on the basis of animal data range from $2.9 \times 10^{-3}/(\mu g/m^3)$ to $4.4/(\mu g/m^3)$. The magnitude of potency appears to depend upon the beryllium compound used in the experiment. Among the four beryllium compounds examined in the eight studies, beryl ore is the least carcinogenically potent, while beryllium sulfate ($BeSO_4$) is the most potent. Except in the case of the beryl ore study (Wagner et al., 1969), the potency values for beryllium that have been estimated on the basis of animal studies are considerably greater than those estimated from human data. A possible explanation is that a specific beryllium compound (e.g., $BeSO_4$) was used in animal experiments, whereas workers were exposed to a combination of several forms of compounds. If one adopts the most conservative approach, the maximum potency estimate $4.4/(\mu g/m^3)$ would be used to represent the carcinogenic potential of beryllium. This potency is estimated on the basis of data obtained in an experiment in which the level of exposure was very similar to the occupational exposure condition. Thus, the high potency estimate is not due to the use of a particular low-dose extrapolation model. The use of such a potency estimate would clearly overestimate the human risk and would be inconsistent with the human experience in the beryllium industry.

Data from two epidemiologic studies by Mancuso (1979) and Wagoner et al. (1980), and the industrial hygiene reviews by NIOSH (1972) and Eisenbud and Lisson (1983), have been used to calculate the cancer risk associated with exposure to air contaminated with beryllium. Three relative risk estimates, 1.67, 1.79, and 2.23, reported in the two epidemiologic studies, have been used by the CAG to calculate the carcinogenic potency of beryllium. Despite the deficiencies in these studies, the use of these relative risk estimates in the calculation is considered appropriate for the reason that, even if the studies were negative, the upper-limit estimates for these relative risks would have been approximately equal to the reported values. In recognition of the greater uncertainty associated with the exposure estimation, four different "effective" levels of exposure that reflect various uncertainties, along with three relative risk estimates, have been used in the present calculations. As a result, 12 potency estimates have been calculated, ranging from 1.1 x $10^{-4}/(\mu g/m^3)$ to 5.0 x $10^{-3}/(\mu g/m^3)$, with the geometric mean of the twelve estimates being 7.4 x $10^{-4}/(\mu g/m^3)$. The incremental lifetime cancer risk associated with 1 $\mu g/m^3$ of beryllium in the air is thus estimated to be 7.4 x 10^{-4}. This estimate could be considered an upper-bound estimate of the cancer risk because low-dose linearity is assumed in the extrapolation. This calculation places the relative carcinogenic potency of beryllium in the lower part of the third quartile of the 53 suspect carcinogens evaluated by the CAG.

7.4 SUMMARY

7.4.1 Qualitative Summary

Experimental beryllium carcinogenesis has been successfully induced by intravenous or intramedullary injection of rabbits, and by inhalation exposure or intratracheal injection of rats. The carcinogenic evidence for mice (intravenously injected), monkeys, and rabbits (intratracheally injected or exposed via inhalation) is presently uncertain. Guinea pigs, and possibly hamsters, are not susceptible to beryllium carcinogenesis. In rabbits, osteosarcomas and chondrosarcomas have been induced. These tumors have been highly invasive and shown to readily metastasize. These tumors have been judged to be histologically similar to corresponding human tumors. In rats, pulmonary adenomas and/or adenocarcinomas of questionable malignancy have been obtained, although these studies are not well documented.

For the purposes of assessing the risks of human exposures to beryllium, the animal evidence has limitations. Despite the fact that osteosarcomas in rabbits were observed in multiple experiments, it is of limited value to assessing human risks because of the artificiality of the intravenous route of administration and the use of complex mixtures of beryllium (zinc beryllium silicate).

Epidemiologic studies present equivocal conclusions on the carcinogenicity of beryllium and beryllium compounds. Early studies (see IARC, 1972, 1980; Bayliss et al., 1971; Bayliss and Lainhart, 1972) did not provide positive evidence, but a few recent studies suggest an increased risk of lung cancer in beryllium-exposed workers. Data presented by Wagoner et al. (1980) indicating significant positive lung carcinogenesis in humans exposed to beryllium have been questioned. In general, the absence of beryllium exposure levels and the lack of information on other possible confounding factors within the workplace make a positive correlation between beryllium exposure and increased risk of cancer difficult to substantiate. Epidemiologic evidence must therefore be classified as "limited" to "inadequate" according to the IARC criteria for determining carcinogenicity from human studies.

Beryllium at the cellular level (precise chemical species unknown) increased the misincorporation of polydeoxyadenosylthymidine into microsomal DNA (Luke et al., 1975) and substantially reduced the fidelity of *in vitro* DNA transcription by single-base substitutions (Sirover and Loeb, 1976).

Dipaolo and Casto (1979) reported the transformation of cultured fetal cells of the Syrian hamster.

Beryllium has been tested for its ability to cause gene mutations in *Salmonella typhimurium*, *Escherichia coli*, yeast, and cultured mammalian cells; chromosomal aberrations, sister chromatid exchanges in cultured human lymphocytes and Syrian hamster embryo cells; DNA damage in *Escherichia coli* and unscheduled DNA synthesis in rat hepatocytes.

Beryllium sulfate and beryllium chloride have been shown to be nonmutagenic in bacterial and yeast gene mutation assays that have been tested. Gene mutation studies in cultured mammalian cells, Chinese hamster V79 cells, and Chinese hamster ovary (CHO) cells, on the other hand, have yielded a positive mutagenic response for beryllium. Similarly, chromosomal aberration and sister chromatid exchange studies in cultured human lymphocytes and Syrian hamster embryo cells have also resulted in positive mutagenic responses of beryllium. In DNA damage and repair assays, beryllium was negative in the *pol*, rat hepatocyte, and mitotic recombination assays but weakly positive in the *rec* assay. Based on the information available, beryllium appears to have the potential to cause mutations.

7.4.2 Quantitative Summary

Both animal and human data are used to estimate the carcinogenic potency of beryllium. Most of the animal inhalation studies for beryllium are not well documented, were conducted only at single dose levels, and did not utilize control groups. In the present report, data from eight rat studies have been used to estimate the upper bounds for the carcinogenic potency of beryllium. The upper-bound potency estimates calculated on the basis of animal data range from $2.9 \times 10^{-3}/(\mu g/m^3)$ to $4.4/(\mu g/m^3)$. The magnitude of potency appears to depend on the beryllium compound used in the experiment. Among the four beryllium compounds examined in the eight studies, beryl ore is the least carcinogenically potent while beryllium sulfate ($BeSO_4$) is the most potent. Except in the case of the beryl ore rat study (Wagner et al., 1969), the potency values for beryllium that have been estimated on the basis of animal studies are considerably greater than those estimated from human data.

In light of the human experience in the beryllium industry, the risk estimates from animal data do not appear to be reasonable. Therefore, information from epidemiologic studies by Mancuso (1979) and Wagoner et al. (1980) and the industrial hygiene reviews by NIOSH (1972) and Eisenbud and Lisson (1983) have been used to estimate the cancer risks associated with exposure to air contaminated with beryllium. The upper-bound incremental lifetime cancer risk associated with 1 $\mu g/m^3$ of beryllium in air is estimated to be $7.4 \times 10^{-4}/(\mu g/m^3)$.

Although there are deficiencies in the epidemiologic studies from which the relative risk estimates are obtained, all of the relative risk estimates have values of approximately 2. Even if all of the studies were negative, a statistical upper-bound estimate of a relative risk would be about equal to the reported value of approximately 2. A major uncertainty of the risk estimate for beryllium comes from the derivation of exposure levels in the workplace and the temporal effect of the patterns of exposure. To account for these uncertainties, the "effective" exposure level of beryllium is derived in several ways, and the geometric mean of different potency estimates thus calculated is used to represent the carcinogenic potency of beryllium.

The upper-bound incremental unit risk of $7.4 \times 10^{4}/(\mu g/m^3)$ places the relative carcinogenic potency of beryllium in the third quartile of the 53 suspect carcinogens evaluated by the CAG.

7.5 CONCLUSIONS

Using the IARC approach (Appendix B) for classifying the weight-of-evidence for carcinogenicity in experimental animals, there is "sufficient" evidence to conclude that beryllium and beryllium compounds are carcinogenic in animals, whereas the epidemiologic evidence for the carcinogenicity of beryllium is "limited" to "inadequate" according to the IARC criteria (Appendix B).

The overall evidence for the carcinogenicity, using the IARC criteria (Appendix B), places beryllium and beryllium compounds in the Group 2A or 2B category, meaning that beryllium is probably carcinogenic to humans under inhalation exposure conditions.

The upper-bound incremental lifetime cancer risk for continuous inhalation exposure at 1 μg beryllium/m^3 is estimated to be 7.4 x 10^{-4}. This means that the actual unit risk is not likely to be higher, but could be lower than 7.4 x 10^{-4}. Also, this places beryllium in the lower part of the third quartile of the 53 suspect carcinogens evaluated by the CAG.

8. HUMAN HEALTH RISK ASSESSMENT FOR BERYLLIUM

8.1 AGGREGATE HUMAN INTAKE OF BERYLLIUM

The intake via ambient air can be estimated to be generally less than 20 ng/day, assuming that 20 m^3 air is inhaled per day. This is a conservative estimate since even in some of the larger industrial cities, average concentrations generally do not exceed 0.2 ng/m^3. Small segments of the population living near beryllium-processing plants may have higher exposure via ambient air since concentrations in such areas may exceed 10 ng/m^3.

There is a lack of data on beryllium in drinking water. There is one estimate of an average concentration of 0.2 μg/l. Assuming a daily intake of 2 l of water, this would mean an intake of 0.4 μg via water. Food normally contains low concentrations of beryllium. The limited data available indicate that the average concentration may be around 0.1 μg/kg fresh weight. Assuming a daily intake of 1200 g of food, this results in a food intake of 0.12 μg/day. Thus, intake via food and water is probably less than 1 μg/day. These estimates are based on the data of Meehan and Smythe (1967). Reeves (1979), however, has estimated, based upon the data of Petzow and Zorn (1974), that food and water may account for intakes up to 20 μg/day.

Regardless of the data base used, exposure via air will constitute only a minor part of the total exposure. Absorption both from the lungs and from the gut is assumed to be relatively small. An additional exposure source may be smoking.

8.2 SIGNIFICANT HEALTH EFFECTS OF BERYLLIUM FOR HUMAN RISK ASSESSMENT

Acute noncarcinogenic effects of beryllium exposure have been exclusively of concern in the workplace, and even with considerable reductions in occupational exposure to beryllium compounds, new cases still appear, indicating that the handling of beryllium must be carefully controlled. The lung is the critical organ of acute exposures and the acute lung effects generally are regarded as reversible, even if, in a few cases, chronic beryllium disease results, especially when further exposures occur.

Chronic effects after exposure to beryllium compounds have been reported to occur both in occupational groups and in members of the general population living in the vicinity of beryllium-emitting plants. In contrast to most other metals, the lung effects caused by chronic exposure to beryllium may be combined with systemic effects, and one common factor may be hypersensitization. Thus, no attempt is made to differentiate between risk estimates for local and systemic effects after chronic exposure to beryllium via air. There are no data that indicate that exposure via food or water can cause such systemic reactions.

The epidemic of chronic beryllium disease which started in the 1940's as a result of heavy exposure resulted in many deaths from chronic lung disease and secondary heart disease (cor pulmonale) and probably also cancer of the lung. Of special interest is that a large number of cases found in the Beryllium Case Registry were "neighborhood" cases. These cases were people living in the vicinity of beryllium-emitting industries, and the clinical manifestations of their disease did not differ from that of occupationally exposed workers. Within the last decades, no new neighborhood cases have been reported to the registry.

It can be concluded that chronic lung disease is a critical effect for exposure to beryllium compounds and preventing this effect will also prevent other effects related to or combined with that condition.

Epidemiological studies present equivocal conclusions on the carcinogenicity of beryllium and beryllium compounds. Such studies have been subject to numerous deficiencies including inadequate considerations of smoking effects and previous exposures to other compounds, as well as underestimations of expected lung cancer deaths resulting in upward biases of relative risks. Nevertheless, the possibility exists that a portion of the excess cancer risks reported in these studies may be due to beryllium exposure.

IARC has concluded that beryllium and its compounds should be classified as "limited" with respect to the human epidemiologic evidence of carcinogenicity and "sufficient" with respect to animal evidence. Overall, the weight of evidence indicates that beryllium and beryllium compounds should be considered as probably carcinogenic for humans.

8.3 DOSE-EFFECT AND DOSE-RESPONSE RELATIONSHIPS OF BERYLLIUM

An attempt has been made to quantify the health impact of beryllium on human beings with reference to potential effects on the U.S. population as a whole. Only chronic effects resulting from long-term low level exposure are discussed, since there is no likelihood of acute effects in the general population. Even though data are sparse on exposure via food and water, it seems very likely that exposure from such sources is very low and that subsequent absorption of beryllium from the intestinal tract is also very low. Therefore, only effects from respiratory exposure are discussed below.

In contrast to some other agents, it is very difficult to use exposure data to construct dose-response curves since the immunological component of chronic beryllium disease indicates that, in addition to direct toxic effects from beryllium in the lung, some people may be at extra risk for effects due to hypersensitization. There is also a lack of data on internal indices of exposure. Information on the levels of beryllium in tissues of the general population is very sparse.

Nevertheless, data collected throughout the years on air concentrations of beryllium in factories and on the occurrence of effects may be used to determine an effect level (dose-response relationship). The standard set in 1949, 2 $\mu g/m^3$ for occupational exposure, can be used as a starting point. When this standard has been exceeded, as reported by Kanarek et al. (1973) and Sprince et al. (1978), clear effects have been noted with regard to pulmonary changes and respiratory function. A drastic reduction of exposure can result in some improvement in pulmonary function, but the data do not allow conclusions about the no-effect level.

In the study by Cotes et al. (1983), the average exposure was stated to be less than or equal to 2 $\mu g/m^3$. However, the data were presented as geometric means, and the arithmetic mean, which is a more appropriate estimate of true exposure, might have been considerably higher. It is true that in several areas studied by Cotes and co-workers, the geometric means were so low that the arithmetic means must also have been well below 2 $\mu g/m^3$. Nevertheless, in that same study, which was based on data collected during an 8-year period with more than 3,000 measurements of beryllium in the air, there were also several periods when peak exposures were above 100 $\mu g/m^3$. It is thus quite conceivable that, of the more than 100 workers studied in the factory, several may have had relatively high exposures during shorter periods. A few cases of verified or strongly suspected chronic beryllium disease were noticed in the factory workers. However, no functional impairment could be found among the workers, in contrast to the study by Kanarek et al., where exposures were much greater. Only the X-ray findings were typical of beryllium exposure. It is therefore reasonable to assume that in the Cotes et al. study, a "no observable adverse effect level" (NOAEL) was found, indicating that the present occupational standard of 2 $\mu g/m^3$ seems to protect against noncarcinogenic toxic effects.

In summary, it appears that it may be impossible to establish dose-response relationships with regard to the noncarcinogenic effects of inhaled beryllium because hypersensitization may occur at random. The present occupational standard, which is far above present levels of beryllium in ambient air, seems to be a reasonable safe level for preventing noncarcinogenic effects in industry.

In Chapter 7, the Carcinogen Assessment Group (CAG) of the U.S. Environmental Protection Agency has estimated carcinogenic unit risks for air exposure to beryllium. The quantitative aspect of carcinogen risk assessment is included here because it may be of use in setting regulatory priorities, evaluating the adequacy of technology-based controls, and other aspects of the regulatory decision-making process. However, the imprecision of presently available technology for estimating cancer risks to humans at low levels of exposure should be recognized. At best, the linear extrapolation model used (see Section 7.3) provides a rough but plausible estimate of the upper limit of risk--that is, with this model it is not likely that the true risk would be much more than the estimated risk, but it could be considerably lower. The risk estimates presented below should not be regarded, therefore, as accurate representations of true cancer risks even when the exposures involved are accurately defined. The estimates presented may, however, be factored into regulatory decisions to the extent that the concept of upper-risk limits is found to be useful.

Although there are many animal inhalation studies showing carcinogenic effects from beryllium, the animal data do not appear to provide an adequate data base for estimating the human cancer risk associated with exposure to beryllium. Most of the animal studies that have been conducted on beryllium are not well documented, were conducted only at single-dose levels, and did not utilize control groups. In the present report, data from several of the more reliable of these animal inhalation studies have been used to calculate the upper bounds for the carcinogenic potency of beryllium. The upper-bound potency estimates calculated on the basis of animal data range from $2.9 \times 10^{-3}/(\mu g/m^3)$ to $4.4/(\mu g/m^3)$, depending on the beryllium compound used in the experiment. Among the four beryllium compounds examined in the seven studies referenced herein, the least carcinogenically potent was shown to be beryl ore, while the most potent was beryllium sulfate ($BeSO_4$). Except in the case of the beryl ore study (Wagner et al. 1969), the potency values for beryllium that have been estimated on the basis of animal studies are considerably greater than those estimated from human data. In light of the human experience in the beryllium industries, the risk estimates from animal data do not appear to be reasonable. Therefore, despite the deficiencies associated with the human data, information from two epidemiologic studies by Mancuso (1979) and Wagoner et al. (1980) and the industrial hygiene reviews by NIOSH (1972) and Eisenbud and Lisson (1983) have been used to estimate the cancer risks associated with exposure to air contaminated with beryllium. The upper-bound incremental lifetime cancer risk associated with 1 $\mu g/m^3$ of beryllium in the air is estimated to be 7.4×10^{-4}. This incremental unit risk estimate places the relative carcinogenic potency of beryllium in the lower part of the third quartile of the 53 suspect carcinogens evaluated by the CAG.

8.4 POPULATIONS AT RISK

Populations at risk may be defined as those segments of the population where there is an increased risk of effects from beryllium, either by virtue of a special exposure status or by some physiological status that renders them more susceptible to the effects of beryllium.

In terms of exposure, persons engaged in handling beryllium in occupational environments obviously comprise individuals at highest risk. With regard to the population at large, there may still be a small risk for people living near beryllium-emitting industries. However, the risk for such individuals may not be due so much to ambient air levels of beryllium, but rather due to the possibility of accumulated beryllium-contaminated dust within the household. There are no data that allow an estimate of the number of people that may be at such risk, but it is reasonable to assume that it is a very small group. It should be noted that no new "neighborhood" cases of beryllium disease have been reported since the 1940's.

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9. REFERENCES

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APPENDIX A

ANALYSIS OF INCIDENCE DATA WITH TIME-DEPENDENT DOSE PATTERN

Table A-1 presents time-to-death data with or without lung tumors. These data are reconstructed from Figure 1 in Reeves and Deitch (1969), in which study animals were exposed to beryllium by inhalation at a concentration of 35 $\mu g/m^3$, 35 hours/week for specific durations during the 24-month observation period.

The computer program ADOLL1-83, developed by Crump and Howe (1984), has been used to fit these data. Models with one to seven stages and with one of the stages affected by the dose have been calculated. The model with the maximum likelihood has been selected as the best-fitting model. The identified best-fitting model has six stages, with the fifth stage dose-affected. Using this model, the maximum likelihood estimate of the slope (linear component), under the assumption of constant exposure, is $0.81/(\mu g/m^3)$. The 95 percent upper confidence limit for the slope is $1.05/(\mu g/m^3)$.

TABLE A-1. TIME-TO-DEATH DATA[a]

Exposure period[b]	Time-to-death
1. Control	19^-, $20^-(2)$, $21^-(6)$, $22^-(8)$, $24^-(8)$
2. 14th - 19th month	$14^-(2)$, 15^-, $20^-(4)$, 20^+, $21^-(5)$, 21^+, $22^-(5)$, $24^-(3)$, 24^+
3. 11th - 16th month	$20^-(2)$, $21^-(5)$, 21^+, 22^-, $22^+(3)$, $24^+(9)$
4. 8th - 13th month	13^-, 14^-, $20^+(2)$, $21^-(5)$, 21^+, $22^+(6)$, $23^-(2)$, $24^-(4)$, $24^+(3)$
5. 5th - 10th month	13^-, $19^-(3)$, $20^+(3)$, $21^-(2)$, $21^+(4)$, 22^-, $22^+(4)$, 23^-, $24^+(3)$
6. 2nd - 8th month	16^-, 17^-, 18^-, $19^-(4)$, $20^-(2)$, 20^+, $21^-(3)$, $21^+(3)$, 22^-, $22^+(6)$, 24^-
7. 8th - 19th month	$15^-(2)$, 17^-, 19^-, $20^-(3)$, $21^-(5)$, $21^+(3)$, $22^-(3)$, $22^+(2)$, $24^-(2)$, $24^+(4)$
8. 2nd - 13th month	14^-, 18^-, $19^-(4)$, $20^+(3)$, $21^+(6)$, $22^+(4)$, $24^+(2)$
9. 2nd - 19th month	16^-, $18^-(4)$, $19^-(2)$, $20^-(5)$, $20^+(3)$, $21^+(3)$, 21^-, 22^+

[a] $t^{+}(n)$ and $t^{-}(n)$ indicate, respectively, the time-to-death with and without lung tumor; n is the number of replications.

[b] All animals were exposed to beryllium at a concentration of 35 μg/m^3, 35 hours/week.

APPENDIX B

INTERNATIONAL AGENCY FOR RESEARCH ON CANCER CRITERIA FOR EVALUATION OF THE CARCINOGENICITY OF CHEMICALS*

ASSESSMENT OF EVIDENCE FOR CARCINOGENICITY FROM STUDIES IN HUMANS

Evidence of carcinogenicity from human studies comes from three main sources:

1. Case reports of individual cancer patients who were exposed to the chemical or process.
2. Descriptive epidemiological studies in which the incidence of cancer in human populations was found to vary in space or time with exposure to the agents.
3. Analytical epidemiological (case-control and cohort) studies in which individual exposure to the chemical or group of chemicals was found to be associated with an increased risk of cancer.

Three criteria must be met before a causal association can be inferred between exposure and cancer in humans:

1. There is no identified bias which could explain the association.
2. The possibility of confounding has been considered and ruled out as explaining the association.
3. The association is unlikely to be due to chance.

In general, although a single study may be indicative of a cause-effect relationship, confidence in inferring a causal association is increased when several independent studies are concordant in showing the association, when the association is strong, when there is a dose-response relationship, or when a reduction in exposure is followed by a reduction in the incidence of cancer.

The degrees of evidence for carcinogenicity from studies in humans are categorized as:

1. Sufficient evidence of carcinogenicity, which indicates that there is a causal relationship between the agent and human cancer.

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*Adapted from International Agency for Research on Cancer Monographs Supplement 4, Evaluation of the Carcinogenic Risk of Chemicals to Humans, 1982, pp. 11-14.

2. Limited evidence of carcinogenicity, which indicates that a causal interpretation is credible, but that alternative explanations, such as chance, bias, or confounding, could not adequately be excluded.

3. Inadequate evidence, which indicates that one of three conditions prevailed: (a) there were few pertinent data; (b) the available studies, while showing evidence of association, did not exclude chance, bias, or confounding; (c) studies were available which do not show evidence of carcinogenicity.

ASSESSMENT OF EVIDENCE FOR CARCINOGENICITY FROM STUDIES IN EXPERIMENTAL ANIMALS

These assessments are classified into four groups:

1. Sufficient evidence of carcinogenicity, which indicates that there is an increased incidence of malignant tumors: (a) in multiple species or strains; or (b) in multiple experiments (preferably with different routes of administration or using different dose levels); or (c) to an unusual degree with regard to incidence, site or type of tumor, or age at onset. Additional evidence may be provided by data on dose-response effects, as well as information from short-term tests or on chemical structure.

2. Limited evidence of carcinogenicity, which means that the data suggest a carcinogenic effect but are limited because: (a) the studies involve a single species, strain, or experiment; or (b) the experiments are restricted by inadequate dosage levels, inadequate duration of exposure to the agent, inadequate period of follow-up, poor survival, too few animals, or inadequate reporting; or (c) the neoplasms produced often occur spontaneously and, in the past, have been difficult to classify as malignant by histological criteria alone (e.g., lung and liver tumors in mice).

3. Inadequate evidence, which indicates that because of major qualitative or quantitative limitations, the studies cannot be interpreted as showing either the presence or absence of a carcinogenic effect; or that within the limits of the tests used, the chemical is not carcinogenic. The number of negative studies is small, since, in general, studies that show no effect are less likely to be published than those suggesting carcinogenicity.

4. No data indicate that data were not available to the Working Group.

The categories, sufficient evidence and limited evidence, refer only to the strength of the experimental evidence that these chemicals are carcinogenic and not to the extent of their carcinogenic activity nor to the mechanism involved. The classification of any chemical may change as new information becomes available.

EVALUATION OF CARCINOGENIC RISK TO HUMANS

At present, no objective criteria exist to interpret data from studies in experimental animals or from short-term tests directly in terms of human risk. Thus, in the absence of sufficient evidence from human studies, evaluation of the carcinogenic risk to humans was based on consideration of both the epidemiological and experimental evidence. The breadth of the categories of evidence defined above allows substantial variation within each. The decisions reached by the Working Group regarding overall risk incorporated these differences, even though they could not always be reflected adequately in the placement of an exposure into a particular category.

The chemicals, groups of chemicals, industrial processes, or occupational exposures were thus put into one of three groups:

Group 1

The chemical, group of chemicals, industrial process, or occupational exposure is carcinogenic to humans. This category was used only when there was sufficient evidence from epidemiological studies to support a causal association between the exposure and cancer.

Group 2

The chemical, group of chemicals, industrial process, or occupational exposure is probably carcinogenic to humans. This category includes exposures for which, at one extreme, the evidence of human carcinogenicity is almost "sufficient," as well as exposures for which, at the other extreme, it is inadequate. To reflect this range, the category was divided into higher (Group A) and lower (Group B) degrees of evidence. Usually, category 2A was reserved for exposures for which there was at least limited evidence of carcinogenicity to humans. The data from studies in experimental animals played an important role in assigning studies to category 2, and particularly those in Group B; thus, the combination of sufficient evidence in animals and inadequate data in humans usually resulted in a classification of 2B.

In some cases, the Working Group considered that the known chemical properties of a compound and the results from short-term tests allowed its transfer from Group 3 to 2B or from Group 2B to 2A.

Group 3

The chemical, group of chemicals, industrial process, or occupational exposure cannot be classified as to its carcinogenicity to humans.